Chronic Obstructive Pulmonary Disease: Abandoning the “Streetlight Effect”

The World Health Organization predicts chronic obstructive pulmonary disease (COPD) to be the third leading cause of death worldwide by 2030 (1). It is well known that there is a correlation between frequent COPD exacerbations and worsened survival (2). Several cohorts have shown that patients with COPD exacerbations have a stronger likelihood of continuing to have exacerbations (3, 4), even though recent data suggest there is significant variability in this exacerbation rate (5). These exacerbations, which are a major cause of morbidity and mortality, are caused in part by bacterial infections (6–9), although there is significant evidence indicating that viral infections also significantly contribute to COPD exacerbations (10–12).

As the interface with the external environment, the lung is crucial in mounting immunological responses against all respired materials, including pathogens and particulate matter. Alveolar macrophages are key sentinels of innate immune response that mediate phagocytic response to these pathogens. Phagocytosis can be divided into nonopsonic or opsonic mechanisms. Although the nonopsonic receptors recognize molecular patterns on the surface that are unique to pathogens during opsonization, pathogens and other particles are coated with opsonizing antibodies or C3b complement, increasing phagocytic efficacy. The costimulation of endocytic pattern recognition receptors and opsonin receptor increases the efficacy of the phagocytic process, enhancing the lysosomal elimination of the infective agent. Opsonization is especially required with clearing capsulated organisms, which include a significant number of microbes involved in COPD exacerbations.

Although previous studies have found defects in nonopsonic mechanisms of phagocytosis in COPD macrophages (13–15), studying phagocytosis in the context of opsonization is paramount, given the clinical relevance of *Streptococcus pneumoniae*. Furthermore, the association of defective phagocytosis with worsened COPD outcomes has been speculated, but it has not been confirmed. In this issue of the *Journal*, Bewley and colleagues (pp. 739–750) found that alveolar macrophages from patients with COPD had impaired ability for opsonic phagocytosis (16). Moreover, the ability to opsonize bacteria was inversely correlated with the rate of exacerbations, and the phagocytic defects of COPD alveolar macrophages were most predictive of COPD severity. This correlation with clinical outcomes was not found with nonopsonized phagocytosis. Previous studies have shown that the transcription factor Nrf2 (nuclear erythroid factor 2–related factor 2) regulates antioxidant and many cytoprotective genes in macrophages, and defects in this pathway may contribute to compromised phagocytosis (13). The treatment with Nrf2 agonists increases nonopsonic and

opsonic phagocytosis in COPD alveolar macrophages, but not in monocyte-derived macrophages, suggestive of a compartmentalized effect.

The article by Bewley and colleagues (16) provided valuable insight on COPD exacerbations. The observed defect in opsonization in COPD alveolar macrophages is noteworthy, as a large number of COPD exacerbations are caused by capsulated organisms such as *S. pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. This association is substantiated by the fact that the defects in opsonization correlate with frequency in COPD exacerbations and patient-related outcomes such as lung function, respiratory status, and distance walked in 6 minutes. However, this correlation is only observed in alveolar macrophages, and not in monocyte-derived macrophages. It is well known that alveolar macrophages and monocyte-derived macrophages function differently. Berenson and colleagues demonstrated that macrophages derived from peripheral blood monocytes of COPD donors had no complement-mediated phagocytic impairment, suggesting a compartmentalized immunologic defect (14). This compartmentalization continues with all types of phagocytosis and shows a fundamental difference in mechanism that occurs in peripheral monocyte-derived macrophages and alveolar macrophages, casting a further shadow on strategies to substitute sampling of peripheral compartments for local ones because of the ease of access.

Similarly, Bewley and colleagues (16) also found that the treatment with the Nrf2 agonists increased both nonopsonic and opsonic phagocytosis in alveolar macrophages derived from patients with COPD, but not in monocyte-derived macrophages. The defect that was found with opsonization was not a result of a lack of available antibodies in the local environment to target the bacteria or problems with the early killing of targeted bacteria. Although Harvey and colleagues previously identified transcriptional effects of sulforaphane (13), Bewley and colleagues (16) provided evidence on alterations in transcriptional responses involving antioxidant defenses, which was reversed with Nrf2 agonists. These Nrf2 agonists also reverse nonopsonized phagocytosis in macrophages, perhaps indicating a common final pathway involving a range of particles, including both opsonized and nonopsonized bacteria and apoptotic bodies dependent on antioxidant defenses, which are perturbed in COPD.

The phagocytic process involves three steps: recognition by receptors of either an opsonized or nonopsonized particle, receptor-mediated actin polymerization leading to internalization and cleavage of the phagosome from the cytoplasmic surface, and intracellular trafficking for phagosomal maturation, which ultimately leads to the degradation of phagosomal contents and the induction of the appropriate immune responses. Harvey and colleagues described that Nrf2 increased phagocytic ability of macrophages by direct upregulation of the scavenger receptor

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MARCO to allow for internalization of the nonopsonized particle (13). This study suggested downstream defects in alveolar macrophage phagocytosis, which are Nrf2 dependent, perhaps related to the intracellular trafficking and degradation of the phagosome or allowing macrophage survival during this degradation processes. It is puzzling that such a downstream process would be divergent in alveolar macrophages compared with peripheral monocyte-derived macrophages, which highlights our limited understanding of the cellular compartments and their function.

What should be our take-home message from this analysis? Our evolving understanding of the immune system in COPD suggests that although there is a systemic defect in macrophage phagocytosis, a specific defect in phagocytosis of opsonized bacteria is observed specifically in alveolar macrophages, and it correlates closely with clinical phenotype in COPD. This defect is amenable to therapeutic targeting with novel inhibitors of the Nrf2 system. However, the broader message is that there is compartmentalization of cellular responses. Just as in the “streetlight effect,” where a lost wallet is searched for under the streetlight because that is the easiest place to search, we have been sampling an easily accessible surrogate compartment such as peripheral blood. Perhaps it is time to rethink this approach and start measuring cellular and molecular derangements in more local compartments. ■

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New Insights into Complicated Grief in Bereaved Family Members Approached for Organ Donation

Organ donation can be a challenging topic to raise with family members of a person who is neurologically dead. The family is often grief-stricken, struggling to accept the loss of a loved one. The stakes are high—one donor can save up to seven lives—and responses can range

from gratitude for the opportunity to help others to distress at the prospect of causing further injury to the body of the deceased.

In this issue of the *Journal*, Kentish-Barnes and colleagues (pp. 751–758) present the latest installment of a series of large, thought-provoking, high-quality French studies that enhance our understanding of end-of-life care for critically ill patients and their family members (1). In a multicentre observational study, the authors surveyed relatives of neurologically deceased patients to learn about their experience with the organ donation process, and then assessed them for symptoms of complicated grief in the months that followed.

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