Human Rhinovirus Inhibits Macrophage Phagocytosis of Bacteria in Chronic Obstructive Pulmonary Disease

More Than a Common Cold

Chronic obstructive pulmonary disease (COPD) results from chronic inflammation, tissue injury, and aberrant repair processes in the respiratory airways. Acute viral and/or bacterial infections cause acute exacerbations. Rhinovirus (RV) infection is the most common viral cause of acute exacerbations in COPD, accounting for approximately 60% of viral acute exacerbations (1). Secondary bacterial infections frequently follow viral infection, resulting in more severe clinical illness with a greater reduction in FEV_1 over FVC and greater length of hospitalization (2).

In this issue of the *Journal*, Finney and colleagues (pp. 1496–1507) provide an important advance by demonstrating that a type A human RV (HRV) infection, HRV16, impairs phagocytosis of two important pathogens in COPD: nontypeable *Haemophilus influenzae* (NTHi) and *Streptococcus pneumoniae* (3). The HRV-associated phagocytic defect was demonstrated for both bacteria in the case of monocyte-derived macrophages (MDMs), but only for NTHi in the case of alveolar macrophages (AMs). Of note, the authors were able to demonstrate viral uptake by AMs challenged *ex vivo*, with cytoplasmic localization of virions. The phagocytic defect was reprised with a Toll-like receptor 3 (TLR3) agonist (polyinosinic:polycytidylic acid) and was a delayed response, requiring approximately 6 hours of HRV incubation. The authors also showed that HRV16 decreased proinflammatory cytokines in COPD MDMs challenged with NTHi. MDMs and AMs from subjects with COPD showed reduced phagocytosis to NTHi and *S. pneumoniae* (in the absence of HRV challenge) as compared with those obtained from healthy donors, and the degree of AM phagocytosis was correlated with MDM phagocytosis and with FEV_1% predicted for both pathogens.

Other models of the interaction between HRV and macrophages are of potential interest. HRV also induces replication-independent activation of TLR2 in mouse macrophages with production of proinflammatory cytokines (4). Conversely, HRV1B reduces CXCL8 (C-X-C motif chemokine ligand 8) production in response to NTHi, with reduced bacterial clearance and prolonged neutrophilic inflammation in mouse lungs (5). In this case, replication-independent viral responses induce degradation of IRAK-1 (IL-1 receptor–associated kinase 1), a key adaptor required for MyD88-dependent TLR signaling, inducing tolerance to bacterial stimuli in AMs.

The data add to the range of viral infections that have been shown to alter macrophage phagocytosis of bacteria, including influenza A virus (6) and HIV-1 infection (7). Whether HRV can replicate in macrophages has been a subject of controversy. Viable virus was detected in MDMs, but only in one in a thousand cells (8). Detection of viable HRV16 in AMs infected *ex vivo* dropped to almost zero within 48 hours (9). In contrast, HRV16 RNA has been detected up to 10 days after infection of AMs. In the study by Finney and colleagues, a TLR3 agonist also inhibited phagocytosis, suggesting that a delayed pattern recognition receptor–mediated response could mediate the defect. Although cytoplasmic localization was described, it is of interest that there was no nuclear localization; therefore, the virologic mechanisms remain incompletely defined. In addition, the basis for a selective effect on COPD macrophages but not healthy macrophages is unclear.

The authors previously described a systemic macrophage phagocytic COPD defect in MDMs whose development is independent of the unique environment of the COPD lung (10). This is in contrast to other reports that suggested phagocytic defects for NTHi in AMs, but not in MDMs (11). The authors suggest that this discrepancy may be ascribed to differences in the use of colony factors in MDM cultures. However, differences among assays are also likely to contribute, with some measuring uptake of heat-killed unopsonized bacteria (3, 10) and others measuring uptake of live bacteria with or without opsonization (11, 12). Although most studies have reported reduced *S. pneumoniae* ingestion (3, 10, 12), Berenson and colleagues did not describe impaired phagocytosis of *S. pneumoniae* in AMs; however, to counteract autolysis in bacterial cultures, the authors elected to study bacteria in stationary rather than mid-log phase growth (13). Of note, Berenson and colleagues assessed phagocytosis by AMs as the percentage of cells ingesting bacteria, rather than a measure of total bacterial uptake in the population. Because most studies have shown that only a subset of macrophages in culture ingest bacteria, this suggests that it may be the level of ingestion by this population that changes rather than the spectrum of cells within a quite heterogeneous population of cells that ingest bacteria. Collectively, these studies suggest that there is a systemic phagocytic defect of bacteria (but not inert particles such as latex beads) compounded by environmental influences, including HRV infection.

Finney and colleagues also found that in patients with mild to moderate COPD, results obtained with MDMs correlated with the degree of AM deficit. The validity of using MDMs to study AMs has long been debated. Recent lineage-tracing experiments suggest that in mice, AMs are derived from embryonic hematopoietic stem cells in the fetal liver and maintained in steady state independently of blood monocytes (14). This emphasizes the importance of validating MDM findings in AMs, as Finney and her team have done. However, the origin of AM populations in the human lung during COPD is still debated. Moreover, the

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plasticity of macrophages cultured outside their environmental niche means that even *ex vivo* studies of human AMs have limitations that may only be resolved in tissue culture models, *ex vivo* ventilated human lungs, or, ultimately, experimental human challenge models.

What are the major implications of this study for patients living with COPD? Conventional teaching has suggested that respiratory tract infections are the result of individual pathogens, usually recently acquired. However, microbiome studies suggest a more complex interplay between pathogens, and that infections result from "dysbiosis," which is often triggered by viral infections. Dysbiosis with broad population-level changes in bacteria is also observed during acute exacerbations in COPD (15). The effects of multipathogen exposure on the phagocytic function of macrophages should be considered. In this regard, the study by Finney and colleagues suggests that HRV could contribute to dysbiosis of the lung microbiome through the phagocytic defect described, thereby promoting acute exacerbations or episodes of community-acquired pneumonia. Therapeutic approaches will need to address ways in which the host response can be recalibrated during these infections and the (as yet unidentified) mechanistic basis of the phagocytic defect can be corrected. This will potentially require early detection of viral respiratory tract infections, as well as targeted interventions to correct the host defect. ■

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