Prior Exposure to Bacteria Attenuates Viral Disease of the Respiratory Tract: A Role for IL-17 and Innate Immune Memory?

It has been recognized for some time that the incidence of asthma and autoimmunity diseases is lower in rural areas of developing countries with higher incidence of infections, especially with helminth parasites (1). This “hygiene hypothesis” has been explained by infection-induced regulatory T cells suppressing pathogenic T cells that mediate autoimmunity and allergy/asthma (1). Furthermore, there is growing evidence that the microbiota of the gut or respiratory tract can modulate innate and adaptive immune responses in the mucosa, and may also shape systemic immunity (2, 3). There is also evidence from experiments in mice that infection with one pathogen can suppress protective immune responses against another (4). Studies in humans have shown that infection with respiratory viruses, such as influenza and respiratory syncytial virus (RSV), can increase susceptibility to bacterial pathogens (5). A report from Schnoeller and colleagues (pp. 194-202) in this issue of the Journal provides a new twist to this story by showing that respiratory infection of neonatal mice with an attenuated Bordetella pertussis can protect against RSV-induced disease in adult life (6). The protective effect of the bacteria was associated with enhanced IL-10 and IL-17 production and enhanced neutrophil and macrophage recruitments to the lungs and interestingly was reversed after neutralization of IL-17.

IL-17 is a proinflammatory cytokine produced by a subtype of CD4 T cells called Th17 cells, but also by cells of the innate immune system, including γδ T cells, natural killer T cells, and innate lymphoid cells (7, 8). IL-17 and Th17 cells play critical roles in many T-cell-mediated autoimmune diseases and have recently been implicated in allergic inflammation associated with asthma, and are now a major drug target for many immune-mediated diseases (9). Antibodies that block IL-17 or cytokines that promote induction of Th17 cells are highly effective against psoriasis and are showing promise in clinical trials with other autoimmune diseases (9). However, blocking IL-17 in patients with Crohn’s disease has been associated with enhanced inflammation and more frequent fungal infections (10). An increased incidence of respiratory tract infection has also been reported after blocking of the Th1/Th17 pathways (11). This is consistent with the role of IL-17–producing Th17 cells and γδ T cells in protective immunity to fungal and extracellular bacterial infection, where they promote recruitment and activation of neutrophils (7). Th17 cells are also induced during infection with intracellular bacteria and viruses,

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but their precise role in antiviral immunity is not clear. Conversely, IL-17 can contribute to infection-induced inflammatory pathology.

Th17 cells are found at high frequency in the lungs during *B. pertussis* infection of mice, where they function with IFN-γ-secretion of CD4 (Th1) cells to recruit and activate neutrophils and macrophages that help to clear *B. pertussis* from the respiratory tract (12). Th17 cells also play a critical role in protective adaptive immunity to *B. pertussis* induced by immunization with acellular pertussis vaccines (aP) (12). Current aP were introduced into most developed countries about 15 years ago as a safer alternative to the more reactogenic whole-cell pertussis vaccines. However, the incidence of pertussis is increasing, with recent epidemics in many countries, including the United States. This has been attributed to waning or ineffective immunity induced by aP. One limitation of aP is that they fail to induce Th1 responses, required for optimum protective immunity against *B. pertussis*. Alternative approaches under consideration include the use of attenuated *B. pertussis* vaccines (13) or aP with adjuvants that promote Th1 as well as Th17 responses (12). The live attenuated strain BPZE1 induces Th1 responses and confers protective immunity against virulent *B. pertussis* in mice and has recently been tested in phase I clinical trials (13).

So the question then arises: how can respiratory exposure to attenuated *B. pertussis* (BPZE1) protect against RSV-induced infection and disease? Schnoeller and colleagues conclude from their study in mice that the protective effect is mediated by IL-17, with a possible role for IL-10 (6), but do not provide evidence of a mechanism. One simple explanation is that IL-17 production by *B. pertussis*-specific CD4 T cells induced by BPZE1 exerts bystander protection against RSV. However, there is no evidence that IL-17 actually mediates clearance of RSV, or if it does, by what mechanism (activation of neutrophils?). Indeed the data in Figure 5F of the article by Schnoeller and colleagues show that blocking IL-17 in RSV-infected mice (without prior infection with BPZE1) does not affect RSV-induced disease measured by weight loss (6). Furthermore, the *B. pertussis*-specific Th17 cells induced in neonatal mice are unlikely to be still producing IL-17 in adult life, well after clearance of the bacteria, and would not be reactivated by RSV antigens. An alternative explanation is that infection with BPZE1...
induces a form of innate immune memory or imprinting of innate immune cells in the respiratory mucosa that modulated the immune responses induced by the subsequent infection with RSV.

The concept of innate immune training or memory is gaining momentum (14). Indeed, there is already some indirect evidence from a study with B. pertussis; intranasal administration of B. pertussis LPS 24–48 hours before challenge with virulent B. pertussis significantly augmented clearance of bacteria from the lungs (15). If protection against RSV in adult mice induced by infection of neonatal mice with BPZE1 is mediated by “innate immune memory,” it would have to persist for at least 6–8 weeks. The role of IL-17 might be explained by the fact that IL-17 is produced in an innate fashion by certain cells, including γδ T cells, natural killer T cells, and type 3 innate lymphoid cells, and here the stimulus is not specific antigen as it is for Th17 cells, but inflammatory cytokine IL-1β and IL-23 produced by other innate immune cells, including macrophages and dendritic cells (8). Thus, respiratory exposure to LPS or other pathogen-associated molecular patterns (PAMPS) in BPZE1 may induce epigenetic reprogramming in resident respiratory macrophages or dendritic cells that affects subsequent exposure of these cells to RSV, resulting in enhanced production of IL-1β, IL-18, and IL-23, which promote innate IL-17 production (Figure 1).

The potential clinical relevance of these findings is that self-limiting respiratory infections with attenuated bacteria or commensal microbes may have a beneficial effect in limiting potentially lethal diseases caused by respiratory viruses, such as RSV, in human infants. In a broader context, these findings add further strength to the idea of innate immune training and that it may be possible to exploit this phenomenon for development of new immunotherapeutics against immune-mediated disease that exclusively target the innate immune system. ■

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References


