The *Bordetella bronchiseptica* Type III Secretion System Inhibits Gamma Interferon Production That Is Required for Efficient Antibody-Mediated Bacterial Clearance

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Several species of pathogenic microorganisms have developed strategies to survive and persist in vital organs which are normally maintained as sterile by the generation of strong immune responses. Here, we report an immunomodulation involving the *Bordetella bronchiseptica* type III secretion system (TTSS) which contributes to bacterial survival in the lower respiratory tract of the host. The prolonged persistence of *B. bronchiseptica* that was observed in gamma interferon (IFN-γ)-/- mice indicates that the efficient clearance of bacteria from the lower respiratory tract requires not only B cells and antibodies but also IFN-γ production. Our data also suggest that interleukin-10 (IL-10)-producing splenocytes are generated early during infection and that IL-10 inhibits IFN-γ-producing cells and delays the clearance of *B. bronchiseptica* from the lungs. The TTSS of *B. bronchiseptica* inhibits the generation of IFN-γ-producing splenocytes and is required for long-term bacterial persistence in the lower respiratory tract in wild-type mice. This suggests that a mechanism involving the modulation of IFN-γ production by the TTSS facilitates *B. bronchiseptica* survival in the lower respiratory tract.

The ability of the immune system to maintain the sterility of vital organs and to quickly eliminate pathogenic microorganisms from these sites is essential for host survival. As such, the lower respiratory tract is normally maintained as sterile by the generation of strong immune responses that can be measured both locally and systemically. The adaptation to such a specialized niche usually involves a specific set of bacterial factors that allow the pathogen to either subvert or survive the host immune responses. The ability of certain microorganisms to persistently colonize the respiratory tract suggests they have the ability to maintain a balance between bacterial-mediated damage and host immune responses.

There are several known mechanisms of bacterial persistence, including antigenic variation, intracellular survival, outer membrane modifications, and immune suppression. A number of pathogens, including *Mycobacterium tuberculosis*, *Bordetella pertussis*, *Leishmania major*, and hepatitis C virus have been observed to induce anti-inflammatory responses to facilitate their persistence (1–3, 16, 22, 27). Pathogens can induce the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor β which inhibit cellular activation and inflammation and thereby contribute to pathogen persistence (1–3, 16, 22, 27). The resulting inhibition of proinflammatory cytokines, such as gamma interferon (IFN-γ), allows the bacteria to persist within the host without inducing significant damage.

Here, the natural host-pathogen model of murine respiratory infection with *Bordetella bronchiseptica* was used to examine potential mechanisms of immunomodulation to facilitate bacterial persistence. *B. bronchiseptica* is a gram-negative respiratory pathogen that naturally infects most mammals (14). Upon experimental inoculation of mice, *B. bronchiseptica* establishes a chronic, asymptomatic infection and is able to persist in the lower respiratory tract for up to 70 days (15, 19, 24, 25). This persistence is facilitated by the expression of virulence determinants during infection. *Bordetella* species possess a variety of virulence determinants that are globally regulated by the BvgAS two-component system (21). Genes under the regulation of this system that are turned on during infection encode toxins, adhesins, and lipopolysaccharide (LPS) modifications (4, 21, 26). Several of these factors, including the type III secretion system (TTSS), are not required for initial colonization but do contribute to the persistence of *B. bronchiseptica* in the lower respiratory tract (30). The well-defined virulence determinants of *B. bronchiseptica*, the extended period of colonization of the lower respiratory tract, and the ability to use an established natural infection model provide an excellent opportunity to study mechanisms of bacterial persistence.

We have previously observed that B cells, and more specifically, antibodies, are critical components required for the natural clearance of *B. bronchiseptica* from the lower respiratory tract (19). Here we extend these studies to show that IFN-γ is also required for efficient clearance of *B. bronchiseptica* from the lower respiratory tract. *B. bronchiseptica* induces the generation of IL-10-producing cells early during infection, and these IL-10-producing cells inhibit the generation of IFN-γ-producing cells, which may delay bacterial clearance. This immunomodulation appears to be mediated by the TTSS of *B. bronchiseptica*, which interferes with the generation of IFN-γ-producing cells that are required for efficient clearance of bacteria from the lower respiratory tract. A Δ*bvg* mutant of *B. bronchiseptica*, which lacks the ATPase required for type III secretion, is defective in persistence compared to the wild-type

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strain, suggesting that the inhibition of IFN-γ by the TTSS may be a strategy to facilitate bacterial survival within the respiratory tract. This suggests that *B. bronchiseptica* may be able to persist within a vital organ of the host by utilizing an immunomodulation strategy to survive the strong immune responses that are generated in the lower respiratory tract.

**MATERIALS AND METHODS**

*Bacteria.* The wild-type strain of *B. bronchiseptica*, RB50, was originally isolated from the nasal cavity of a rabbit and has been described elsewhere (5). The ΔnocV mutant was created by the deletion of the bctN gene, an ortholog of yscN, which encodes the ATPase required for the secretion of TTSS-associated proteins, and has been described elsewhere (31). Bacteria were maintained on Bordet-Gengou agar (Difco) supplemented with 10% sheep blood and 20 μg/ml streptomycin. Bacteria were grown to mid-log phase in Stainer-Scholte medium. Bacterial density was calculated based on the optical density at 600 nm and bacteria were diluted to 1 × 10⁶ CFU/ml in sterile phosphate-buffered saline (PBS). Inocula were confirmed by plating dilutions for colony counts. Statistical significance was determined using Student’s t test.

*Mice.* C57BL/6, Igh-6⁻/⁻ (γM), IL-10⁻/⁻, and IFN-γ⁻/⁻ mice were obtained from Jackson Laboratories. All knockout mouse strains are on a C57BL/6 background. For inoculation, mice were lightly sedated with isoflurane (Abbott Laboratories) and 5 × 10⁶ CFU of bacteria in a 50-μl volume were inoculated onto the external nares. For adoptive transfer of serum antibodies, the indicated amount of either serum collected from naive mice or serum collected from convalescent mice on day 28 postinoculation (immune serum), which contains *B. bronchiseptica*-specific antibodies, was injected intraperitoneally at indicated time points. To determine bacterial numbers in the respiratory tract and obtain splenocytes, mice were euthanized by CO2 and the appropriate organs were excised for analysis. Animals were maintained in the animal care facility at Penn State University and all experiments were carried out in accordance with institutional guidelines.

*Bacterial numbers.* To determine bacterial numbers in the lungs, mice were intranasally inoculated as described above and euthanized at the indicated time points. Lungs were excised and homogenized in sterile PBS. Aliquots were diluted in PBS and plated on Bordet-Gengou agar containing 20 μg/ml streptomycin, and colonies were enumerated after 2 days of incubation at 37°C. Statistical significance was determined using Student’s t test.

*Splenocyte restimulations.* Splenocytes were purified by homogenizing spleens through a wire sieve, pelleting the cells by centrifugation at 700 g and then using the supernatant for restimulations. The cells were resuspended in Dulbecco’s modified Eagle medium. The cells were resuspended in Dulbecco’s modified Eagle medium supplemented with 10% fetal calf serum (HyClone), 1 mM sodium pyruvate (HyClone), 100 μg/ml penicillin and streptomycin (HyClone), and 0.005% beta-mercaptoethanol. The cells were counted, and approximately 2 × 10⁶ cells were placed into each well in a 96-well plate. The splenocytes were exposed to medium alone or restimulated by the addition of approximately 2 × 10⁶ heat-killed (HK) *B. bronchiseptica* cells per well. After 3 days of incubation, the supernatant was collected and analyzed for cytokine production as described below. The concentrations of cytokines produced by the control splenocytes which received only medium as well as the splenocytes exposed to HK *B. bronchiseptica* are indicated. Statistical significance was determined using Student’s t test.

*Antibody and cytokine detection.* For detection of *B. bronchiseptica*-specific antibodies, serum collected from C57BL/6 convalescent mice on day 28 was analyzed by enzyme-linked immunosorbent assay (ELISA) as previously described, using secondary antibodies specific for mouse immunoglobulin (Ig) isotypes (Southern Biotechnology Associates) (5). Detection of *B. bronchiseptica*-specific antibodies in the lungs was achieved by Western blotting. Lysate of *B. bronchiseptica* was run on a 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gel and transferred onto an Immobilon polyvinylidene difluoride membrane (Millipore). The membrane was then probed with lung homogenate from *B. bronchiseptica*-infected mice, as the primary probe, and a horseradish peroxidase-conjugated anti-mouse Ig secondary antibody (Southern Biotechnology). An ECL Western blotting detection kit (Amersham Bioscience) was used to develop the blot. Cytokine concentrations were determined by ELISA for IFN-γ and IL-10 using matched antibody pairs (R&D Systems). Statistical significance was determined using Student’s t test.

**RESULTS**

*B. bronchiseptica*-specific antibodies are unable to clear bacteria from the lower respiratory tract on day 28 postinoculation. The ability of *B. bronchiseptica* to persistently colonize the lungs for up to 70 days following experimental inoculation suggests that this species has evolved mechanisms to facilitate its survival even in the presence of significant innate and adaptive immune responses (Fig. 1A). We have previously shown that B cells and antibodies are critical components required to eliminate *B. bronchiseptica* from the lower respiratory tract (19). Significant levels of *B. bronchiseptica*-specific antibodies were detectable in both serum and lung samples from wild-type mice inoculated with *B. bronchiseptica* by day 28 postinoculation, suggesting that both localized and systemic immune response have been mounted by this time point (Fig. 1B and C). *B. bronchiseptica*-specific antibodies were not detectable in the serum or lung samples of uninfected mice (data not shown). Adoptive transfer of 200 μl of immune serum, which was collected from wild-type mice on day 28 postinoculation and contained *B. bronchiseptica*-specific antibodies, into a naïve mouse immediately following inoculation resulted in complete clearance of the bacteria from the lower respiratory tract within 3 days (Fig. 1A). Further analysis of this clearance, using immune serum that was fractionated using protein G columns, indicates that the *B. bronchiseptica*-specific IgG fraction is sufficient to clear bacteria from the lungs within 3 days following inoculation and serum transfer as described above (data not shown). These data indicate that *B. bronchiseptica* antibodies, and specifically, IgG, are sufficient to mediate clearance in this adoptive transfer model. Together, these data suggest that although sufficient titers of antibodies are present by day 28, these antibodies are unable to eliminate *B. bronchiseptica* from this site until approximately day 70 postinoculation. This presents a notable paradox and suggests that antibody-dependent mechanisms of clearance may be inhibited in order to facilitate bacterial survival within the respiratory tract.

**IL-10-producing cells are generated at early time points during *B. bronchiseptica* infection.** During a typical bacterial infection, T-cell subsets specific for antigens respond by producing a variety of cytokines that serve to shape the subsequent immune response. *B. pertussis*, a closely related species to *B. bronchiseptica*, has previously been observed to modulate the cytokine response by inducing IL-10-producing regulatory T cells to mediate bacterial persistence during the early stages of infection (22, 27). Since *B. pertussis* is known to modulate the cytokine response during infection, we sought to define what cytokines are generated during the course of *B. bronchiseptica* infection. To determine whether IFN-γ, IL-4, IL-6, IL-10, or IL-12-producing cells are generated during *B. bronchiseptica* infection, groups of three wild-type mice were intranasally inoculated with 5 × 10⁶ CFU of *B. bronchiseptica* as described above. On days 0, 3, 7, 14, 21, 28, 49, and 70 postinoculation, the mice were sacrificed and the spleens were excised. Purified splenocytes were then exposed to either medium alone or medium containing HK *B. bronchiseptica* at a multiplicity of infection of 10 for 3 days. The culture supernatant was collected and analyzed for IFN-γ, IL-4, IL-6, IL-10, or IL-12 by ELISA. Very little production of IL-4, IL-6, or IL-12 was detected from cells exposed to either medium alone or me-
lung homogenate collected from mice on days 0, 7, 14, and 28 postinoculation. Data are shown for one of two replicates, which both gave similar results. Values are represented as the means ± standard errors. (C) Western blot of infected C57BL/6 mice. Values are represented as the means ± standard errors. The dashed line indicates the limit of detection.

To determine whether IFN-γ or IL-10 has any effect on the clearance of B. bronchiseptica from the lower respiratory tract, groups of wild-type C57BL/6, IFN-γ−/−, and IL-10−/− mice were intranasally inoculated with 5 × 10^5 CFU of B. bronchiseptica as previously described. On days 0, 3, 7, 14, 28, 49, 70, and 105 postinoculation, the mice were sacrificed and the respiratory organs were excised for analysis of bacterial numbers. On days 14, 28, 49, 70, and 105, the IFN-γ−/− mice had approximately 10- to 100-fold higher numbers of B. bronchiseptica in the lower respiratory tract compared to wild-type C57BL/6, IFN-γ−/−, and IL-10−/− mice. The increasing IFN-γ production from splenocytes collected at later time points correlates with clearance of B. bronchiseptica from the lower respiratory tract, suggesting that IFN-γ may be involved in the clearance of B. bronchiseptica.

The clearance of B. bronchiseptica from the lower respiratory tract is enhanced by IFN-γ and inhibited by IL-10. To determine whether IFN-γ or IL-10 has any effect on the clearance of B. bronchiseptica from the lower respiratory tract, groups of wild-type C57BL/6, IFN-γ−/−, and IL-10−/− mice were intranasally inoculated with 5 × 10^5 CFU of B. bronchiseptica as previously described. On days 0, 3, 7, 14, 28, 49, 70, and 105 postinoculation, the mice were sacrificed and the respiratory organs were excised for analysis of bacterial numbers. On days 14, 28, 49, 70, and 105, the IFN-γ−/− mice had approximately 10- to 100-fold higher numbers of B. bronchiseptica in the lower respiratory tract compared to wild-type C57BL/6 mice. This suggests that IFN-γ contributes to the clearance of B. bronchiseptica from the lower respiratory tract. In contrast, on days 7, 14, 28, and 49 postinoculation, the number of bacteria in the lower respiratory tract of IL-10−/− mice was 1/10th to 1/100th of that of wild-type mice, suggesting that IL-10 inhibits the clearance of B. bronchiseptica from the lower respiratory tract.
To determine whether the faster clearance observed in the IL-10−/− mice may be attributed to increased antibody production, C57BL/6 and IL-10−/− mice were intranasally inoculated with 5 × 10^5 CFU of B. bronchiseptica as previously described, and serum was collected on day 28 postinoculation. B. bronchiseptica-specific serum antibody titers were then measured by ELISA. Unlike C57BL/6 mice, which had high titers of B. bronchiseptica-specific antibodies in the serum on day 28 postinoculation, IL-10−/− mice had significantly lower titers (Fig. 3B). This suggests that the faster clearance of B. bronchiseptica in the IL-10−/− mice is not due to higher antibody production. In addition, since B cells and antibodies are required for the clearance of B. bronchiseptica, this also suggests that antibodies may be more effective in clearing bacteria from the lungs in the absence of IL-10.

**IL-10 inhibits the generation of IFN-γ-producing splenocytes.** Consistent with its anti-inflammatory role, one of the known functions of IL-10 is to inhibit production of proinflammatory cytokines, including IFN-γ (6, 9, 10, 13, 17, and 23). IL-10−/− mice are known to have higher levels of IFN-γ production in a number of infection models (6, 13, 17). Since IFN-γ contributes to the clearance of B. bronchiseptica from the lungs, we hypothesized that the IFN-γ response during B. bronchiseptica infection will be higher in the absence of IL-10 and that this may contribute to the faster clearance of bacteria in IL-10−/− mice. To address this hypothesis, groups of IL-10−/− mice were intranasally inoculated with 5 × 10^5 CFU of B. bronchiseptica as described above, and splenocyte restimulations were performed at days 3, 7, 14, and 28 postinoculation. As previously described, splenocytes from infected IL-10−/− mice were able to produce significantly higher amounts of IFN-γ than were wild-type splenocytes, even in the absence of stimulation with HK bacteria (2,043 ± 93.7 pg/ml). When restimulated with HK bacteria, splenocytes from B. bronchiseptica-infected IL-10−/− mice were able to produce between 10- and 50-fold higher amounts of IFN-γ than splenocytes from wild-type C57BL/6 infected mice (Fig. 4). These results indicate that IL-10 inhibits the IFN-γ response to B. bronchiseptica and are consistent with other data indicating that high levels of IFN-γ may contribute to bacterial clearance from the lower respiratory tract.

**The TTSS inhibits the generation of IFN-γ-producing splenocytes and is required for persistence in the lungs of wild-type mice.** Since the production of IFN-γ correlates with bacterial clearance, this may be a potential target by which B. bronchiseptica may modulate the immune response to favor its persistence. Previous work with the TTSS of B. bronchiseptica suggests that this virulence factor may modulate dendritic cell maturation during infection, leading to a “semimature” dendritic cell phenotype (29). In addition, the TTSS has recently been reported to interact with dendritic cells, resulting in IL-10 production by T-cells both in vitro and in vivo (28). This suggests a model in which the TTSS may serve to induce IL-10 production which inhibits the IFN-γ production required for the clearance of B. bronchiseptica from the lower respiratory tract. To examine whether the TTSS can inhibit the generation of IFN-γ-producing cells, wild-type C57BL/6 mice were intra-
nasally inoculated with $5 \times 10^5$ CFU of either wild-type *B. bronchiseptica* or a $\Delta$bscN mutant strain which lacks the ATPase required for type III secretion. On days 3, 7, 14, 21, and 28, splenocytes were collected for restimulations. Supernatants from splenocytes collected from wild-type (0.0006 ± 22.5 pg/ml) or $\Delta$bscN-infected (0.0003 ± 16.2 pg/ml) mice produced little IFN-γ when cultured with medium alone. Analysis of the culture supernatant from splenocytes that were exposed to HK bacteria indicated that splenocytes collected from the *B. bronchiseptica*-infected mice produced little IFN-γ at the time points examined. In contrast, splenocytes collected from the mice inoculated with the $\Delta$bscN strain on day 7 postinfection produced almost 10-fold higher levels of IFN-γ upon restimulation with HK bacteria (Fig. 5A). This suggests that the TTSS inhibits the production of IFN-γ from restimulated splenocytes.

Since the TTSS has previously been implicated in *B. bronchiseptica* persistence in the trachea and we have shown that the TTSS modulates the IFN-γ response during infection, we next sought to determine whether the TTSS also contributes to *B. bronchiseptica* persistence in the lungs. Groups of wild-type C57BL/6 mice were intranasally inoculated with $5 \times 10^5$ CFU of either wild-type *B. bronchiseptica* or the $\Delta$bscN mutant strain, and bacterial numbers in the lungs were measured on days 0, 3, 7, 14, and 28 postinoculation. Bacterial numbers in the lungs indicate that on days 7, 14, 21, and 28 postinoculation, the $\Delta$bscN mutant was present at only 1/10th to 1/100th of the numbers of wild-type *B. bronchiseptica* (Fig. 5B). Furthermore, unlike wild-type *B. bronchiseptica*, which persists in the lungs for up to 70 days postinoculation, the $\Delta$bscN mutant is almost cleared from the lower respiratory tract by day 28 postinoculation. These data indicate that the TTSS is required for bacterial persistence in the lungs of wild-type mice and suggest that the inhibition of IFN-γ-producing cells by the TTSS may contribute to *B. bronchiseptica* persistence in the lungs.

**DISCUSSION**

Since *B. bronchiseptica* is highly adapted to the mammalian respiratory tract and is able to persist in the lower respiratory tract for up to 70 days following experimental inoculation, we explored the hypothesis that this species modulates the immune response to favor its survival in the host. During the early stages of infection, when *B. bronchiseptica* is able to persist, the cytokine response appears to be mainly IL-10 mediated, while at later time points during bacterial clearance, IFN-γ production is increased. In addition, IL-10$^{-/-}$ mice clear *B. bronchiseptica* from the lower respiratory tract faster, while IFN-γ$^{-/-}$ mice exhibit defective clearance of *B. bronchiseptica* compared to wild-type mice. Together, these data suggest that IL-10 production inhibits the clearance of *B. bronchiseptica* from the lower respiratory tract, while IFN-γ production contributes to bacterial clearance.

Since IL-10 downregulates inflammation by inhibiting chemokine and cytokine secretion as well as the expression of costimulatory molecules, the early IL-10 response during *B. bronchiseptica* infection would likely not only suppress IFN-γ production but also reduce the ability of cells to phagocytose and kill the bacteria (9–12, 23). Conversely, the ability of IFN-γ to mediate the clearance of *B. bronchiseptica* could arise from a number of mechanisms including an increase in either cellular activation or recruitment to the lungs. Treatment of cells with IFN-γ yields an increase in the transcription of a number of known activation markers including the LPS-binding protein CD14, proinflammatory cytokines, and cell surface receptors such as CR3, FcγRI, and FcγRIII, as well as chemokine receptors and costimulatory molecules involved in antigen presentation (7, 8, 18). In addition, the production of reactive oxygen species is increased in response to IFN-γ and is probably responsible for the enhanced efficiency of phagocytic killing of IFN-γ-stimulated cells observed with a variety of microorganisms (reviewed in reference 8). Taken together, this implies that the production of IFN-γ may increase cellular recruitment and/or activation in the lungs, which, in the presence of antibodies, mediates bacterial clearance.

This model agrees with other experimental findings which indicated that a neutrophil-mediated CR3- and FcγR-dependent phagocytic killing mechanism is involved in the clearance of *B. bronchiseptica* when antibodies are injected immediately following inoculation (19, 25). Clearance of bacteria in this model depends on the TLR4-mediated response to LPS which induces the initial recruitment and activation of neutrophils in the lungs (20). In the presence of adoptively transferred antibodies, these cells are able to clear *B. bronchiseptica* from the...
lower respiratory tract within 3 days (20). However, later in the course of infection, cellular recruitment and activation in the lungs may be dampened by both the LPS tolerance effect and the generation of IL-10-producing cells. Eventually, IFN-γ-producing cells may overcome this effect and lead to bacterial clearance via antibody-dependent mechanisms. The data presented here suggest that the TTSS-mediated inhibition of IFN-γ production allows B. bronchiseptica to persist for several weeks after endogenous antibodies are produced.

The ability to alter the levels of proinflammatory and anti-inflammatory cytokines has been described as a strategy for the persistence of several pathogens (1–3, 16, 22, 27). These strategies typically involve the induction of IL-10-producing regulatory T cells which inhibit the inflammation required for the clearance of the microorganism. Interestingly, Bordetella pertussis, the causative agent of whooping cough in humans and a close relative of B. bronchiseptica, is one of the organisms known to utilize this strategy (16, 22, 27). In the case of B. pertussis the generation of IL-10-producing regulatory T cells has been reported to be mediated by an interaction of filamentous hemagglutinin, adenylate cyclase, and LPS with dendritic cells (16, 22, 27). Recent work by Skinner et al. has demonstrated that an interaction of the TTSS of B. bronchiseptica with antigen-presenting cells induces the generation of IL-10-producing splenocytes (28). Our data indicate that in the absence of IL-10, IFN-γ-producing splenocytes are generated at early time points, suggesting that the inhibition of IFN-γ production may occur by a TTSS-dependent induction of IL-10-producing regulatory T cells.

Although the TTSS inhibits IFN-γ production and IFN-γ contributes to bacterial clearance in this model, the TTSS may have other roles that contribute to B. bronchiseptica persistence in the lower respiratory tract. To assess whether the TTSS contributes to B. bronchiseptica persistence in the absence of IFN-γ and IL-10, we measured bacterial numbers in the lungs of IFN-γ−/− and IL-10−/− mice following inoculation with either the wild-type or ΔbscN mutant strain of B. bronchiseptica. In IFN-γ−/− mice, the ΔbscN mutant was recovered in lower numbers than the wild-type B. bronchiseptica strain on day 14 postinoculation. This indicates that in the absence of IFN-γ the TTSS is still required for persistence in the lower respiratory tract and suggests that the TTSS may have some function other than the modulation of IFN-γ responses. The numbers of wild-type and ΔbscN mutant B. bronchiseptica present in the lungs of IL-10−/− mice on day 14 postinoculation were inconsistent from experiment to experiment. This once again suggests that although the TTSS modulates IFN-γ responses during infection, this is not the only role of the TTSS contributing to the persistence of B. bronchiseptica in the lower respiratory tract.

Remarkably, B. bronchiseptica and B. pertussis utilize different bacterial factors to similarly modulate the function of antigen-presenting cells to facilitate bacterial persistence. Both IL-10 and IFN-γ production are tightly regulated during an immune response to facilitate bacterial clearance while limiting inflammation-induced damage to the host. The evolution of specific virulence factors that alter the progression of proinflammatory and anti-inflammatory cytokines gives pathogenic microorganisms the critical ability to persist in immunologically protected sites such as the lower respiratory tract.

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