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The Contrasting Roles of T Regulatory Cells in Bacterial Lung Diseases

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1. Introduction

The respiratory environment is exposed to a variety of different pathogens and irritants from the environment. We breathe in about 10,000 liters of air per day. As such, the immune cells along the respiratory tract constantly come into contact with pathogens and potential immunogens within the air. Since development of inflammatory responses to all these stimuli could result in persistent host responses and inflammation that could eventually be damaging to the lungs, the responses to potential respiratory pathogens, antigens and irritants must be tightly regulated and in some cases tolerated. Ideally, inflammatory responses should only occur when other initial mechanisms of protection, e.g. mucus, mucociliary clearance and phagocytes, are insufficient. Thus, in addition to the ability to differentiate between self and foreign antigens, as is done throughout the rest of the body, respiratory immune responses must also have the capacity to differentiate between harmful and innocuous antigens.

Regulatory mechanisms throughout the body have evolved to control these immune and inflammatory responses, normally allowing for an immune response strong enough to deal with dangerous pathogens, but not so aggressive as to result in harmful immunopathology. Strong suppression by these regulatory mechanisms has been implicated in the pathogenesis of cancer, while weak suppression has been suggested to contribute to autoimmunity. In the lungs, mechanisms have evolved to similarly modulate host responses. This includes surfactants and alveolar macrophages that dampen host immune responses. Lymphocyte populations can also regulate pulmonary immune responses. The lymphocyte population most commonly associated with regulation of host immune and inflammatory responses, including tolerance to innocuous antigens, is the regulatory T (T_{reg}) cell. Although much research has been done in the role of T_{reg} cells in the pathogenesis of asthma, relatively little work has been performed examining these mechanisms in the context of bacterial infections, but the limited studies demonstrate that they can have a significant impact on these diseases. In this article, we will first briefly review the immune environment of the lung and the T_{reg} cells and their function. We then focus on some bacterial lung diseases and what is known about the impact of T_{reg} cells. Specifically, we will examine the potential for T_{reg} cells to have both positive and negative effects on disease progression, depending upon the pathogen.

2. The pulmonary immune environment

The lung is exposed to a variety of different pathogens and irritants from the environment. It would be harmful to the host if immune and inflammatory responses were generated in response to these agents, as it could result in constant inflammation and tissue destruction. Therefore, immune responses must be tolerant of these organisms so as not to upset the equilibrium that exists in the mucosal environment (Sansonetti, 2011). This requires a delicate balance between T_{reg} cells and proinflammatory cells (Sansonetti, 2011).

Research suggests that the lung environment tends to preferentially mount T helper type 2 responses (Th2), though this is not absolute (Constant et al., 2000). The type of immune response elicited during bacterial infection is somewhat dependent on the site of infection, and the size of the antigen dose (Constant et al., 2000; Morokata et al., 2000). In addition, the type of antigen encountered by toll-like receptor-expressing cells can also determine the nature of the resultant immune response (Pulendran, 2004; Wissinger et al., 2009). Toll-like receptors are traditionally associated with antigen presenting cells, such as dendritic cells, macrophages, and B cells, though toll-like receptor stimulation on T helper cells has also been demonstrated to play an important role (Kawai & S. Akira, 2011; Palusinska-Szyszk & Janczarek, 2010; Wissinger et al., 2009).

3. Regulatory T cells

T_{reg} cells are a heterogeneous T cell population thought to maintain immunologic balance and prevent or minimize tissue damaging immune responses (Fehervari & Sakaguchi, 2004a; Fehervari & Sakaguchi, 2004b; Sakaguchi, 2000, 2002, 2003). T_{reg} cells are a subset of $CD4^+$ T cells that make up anywhere from 1-10% of all $CD4^+$ cells in the thymus, blood, and lymph (McHugh & Shevach, 2002). Unlike traditional T helper (Th) cells, T_{reg} cells act to suppress or dampen the immune response. While evidence indicates that other cell populations may also have suppressive capabilities, such as natural killer T cells, gamma-delta ($\gamma\delta$) T cells, and $CD8^+$ suppressor cells, classical T_{reg} cells are by far the most highly studied, the best understood, and, as far as the current evidence indicates, the most important in controlling the body's immune responses (Bach, 2003; Born et al., 2000; Oh et al., 2008; Wang & Alexander, 2009).

Very early on, T_{reg} cells were implicated in autoimmune disorders. A lack of T_{reg} cells was thought to be at least related to the onset of autoimmunity, if not the principal cause of it (Ellner, 1981). To date, T_{reg} cell numbers have been found to be either abnormally low or poorly functioning in patients suffering from diseases such as lupus, rheumatoid arthritis, and myasthenia gravis (Flores-Borja et al., 2008; Mudd et al., 2006; Wang et al., 2008). Laboratory experiments have shown that adoptive transfer of T_{reg} cells into lab animals prone to type I diabetes results in improved prognosis and delay of disease onset (Sakaguchi et al., 2006). Overall, these cells inhibit a wide range of autoimmune and inflammatory reactions, such as gastritis, oophoritis, orchitis, thyroiditis, inflammatory bowel disease (IBD), and spontaneous autoimmune diabetes.

However, in some situations, T_{reg} cells may restrict the actions of the immune system too much. The presence of T_{reg} cells has been suggested to contribute to the progression of cancer. Again, laboratory experiments have shown that depletion of T_{reg} cells can result in

enhanced killing of tumor cells by the immune response (Nomura & Sakaguchi, 2005). Similarly, T_{reg} cells were also shown to contribute to the persistence of *Leishmania major* infection (Belkaid, 2003; Mendez et al., 2004). It is thought that T_{reg} cells suppress the protective immune responses against cancer and some pathogens, resulting in prolonged disease. Furthermore T_{reg} cells can suppress the cytokine production and proliferation of conventional Th cells (Jonuleit et al., 2001; Thornton & Shevach, 1998), but the T_{reg} cells' effects on Th cell subsets are conflicting with some studies (Stassen et al., 2004) suggesting dampening of Th2 responses and others (Suto et al., 2001) indicating promotion of Th2 cell responses. As a result, Treg cells may in some circumstances promote immune responses with varied results. Thus, Treg cells can have both positive and negative impacts on host responses in disease, highlighting the potential dual nature of T_{reg} cells.

First studied in the 1970's, T_{reg} cells, known then as suppressor T cells, were identified based on their ability to suppress antigen-specific immune responses. At that time, it was very difficult to study T_{reg} cells due to the lack of any known markers specific to the cell type. As a result, the existence of T_{reg} cells remained a very controversial idea for a long time. In 1995, it was shown by Sakaguchi et al. that T_{reg} cells constitutively express the interleukin (IL)-2 receptor alpha chain, CD25, at a high level (Nomura & Sakaguchi, 2005). The expression of the IL-2 receptor chain which is normally associated with activated T cells was theorized to be due to the continued T cell receptor engagement of self-antigens by these T_{reg} cells, resulting in a perpetually active state. Thus, the characterization of T_{reg} cells as CD4⁺CD25^{hi} cells became widely accepted. Still, it remained somewhat difficult to distinguish T_{reg} cells from activated Th cells, which also can express CD25, albeit at lower levels. Recently, the association of the intracellular transcription factor forkhead P3 (FoxP3) with T_{reg} cells has led to the most accurate characterization of these cells to date: CD4⁺CD25^{hi}FoxP3⁺ (Hori et al., 2003). CD4⁺CD25^{hi}FoxP3⁺ T_{reg} cells also have other distinguishing surface markers such as GITR, CTLA-4, CD103, CCR4, CD62L, and CD127^{lo}; however, the evidence that these markers are useful to phenotype T_{reg} cells has yet to be established (Bayer et al., 2008; Fu et al., 2004; Liu et al., 2006; Sather et al., 2007; Shimizu et al., 2002; Wing et al., 2008; Zhao et al., 2008).

The mechanisms through which T_{reg} cells exert their suppressive effects throughout the host appear to be numerous, and are likely dependent on the same factors that affect the typical immune response, such as the antigen dose, the nature of the pathogen or allergen, and the route of entry. The most common mechanism observed in both *in vitro* and *in vivo* experiments is secretion of cytokines, particularly IL-10 and transforming growth factor (TGF)- β (Bluestone & A. K. Abbas, 2003; Vignali et al., 2008; von Boehmer, 2005). Both of these cytokines are associated with Th2 responses, and, as such, are at odds with the more common Th1 response. Therefore, secretion of these cytokines by T_{reg} cells reduces or dampens Th1 inflammatory responses. However, these are not the only cytokines that have been associated with T_{reg} cells. IL-35, a member of the IL-12 family of cytokines, has recently been shown to play a role in T_{reg} cell-mediated suppression (Chaturvedi et al., 2011; Collison et al., 2007; Collison et al., 2010). IL-35 is thought to be secreted only by T_{reg} cells, and, while it is known to have a potent anti-inflammatory effect, the mechanism through which it exerts this effect is still poorly understood (Chaturvedi et al., 2011; Collison et al., 2007; Collison et al., 2010). In addition, recent experiments have suggested that T_{reg} cells may also be able to suppress Th2 immune responses through the secretion of interferon (IFN)- γ and

IL-17, though this is still being studied (Ayyoub et al., 2009; Beriou et al., 2009; Esposito et al., 2010; Fang et al., 2009; Voo et al., 2009).

Recent research has also shown that T_{reg} cells may be able to exert suppression through galectin-1, which may be secreted or membrane-bound (Garin et al., 2007; Shevach, 2009). Galectin-1 has been implicated in cell cycle arrest, inhibition of proinflammatory cytokines, and even apoptosis of responder cells, though the mechanism remains unclear (Garin et al., 2007; Shevach, 2009). Blockade of galectin-1 has been shown to abrogate suppression in both human and murine suppressive assays (Garin et al., 2007; Shevach, 2009).

Direct killing of responder cells has also been proposed as a mechanism through which T_{reg} cells can suppress immune responses (Cao et al., 2007; Shevach, 2009). T_{reg} cells have been shown to express perforin, granzyme A, and granzyme B under certain conditions (Cao et al., 2007; Shevach, 2009). T_{reg} cells that express this phenotype have been implicated in cytotoxicity of natural killer cells, T cells, and B cells (Cao et al., 2007; Shevach, 2009). Fas-FasL interaction has also been observed as a suppressive mechanism of T_{reg} cells (Gorbachev & Fairchild, 2010; Strauss et al., 2009). Specifically, stimulation through Fas-FasL coupling has been shown to result in apoptosis of B cells and CD8 T cells in humans (Janssens et al., 2003; Strauss et al., 2009). In addition, there is evidence suggesting that T_{reg} cells can interfere with priming of dendritic cells through Fas-FasL interaction, though it is not clear whether or not this involves cytotoxicity (Gorbachev & Fairchild, 2010).

Other mechanisms that involve T_{reg} cell interference with antigen-presenting cells have also been observed. T_{reg} cells constitutively express CTLA-4, which binds the costimulatory molecules CD80 and CD86 (Shevach, 2009). The role of CTLA-4 is not clear, but there are a number of theories as to how it may function. First, CTLA-4 engagement of CD80 and CD86 may restrict the further expression of costimulatory molecules by antigen-presenting cells (Onishi et al., 2008). Second, CTLA-4 may actually signal antigen-presenting cells to downregulate the expression of CD80 and CD86 (Onishi et al., 2008; Shevach, 2009). Third, the binding of CTLA-4 may simply block CD80 and CD86 from interacting with other cells, thus preventing the delivery of costimulatory signals (Shevach, 2009).

The expression of LAG-3, a homolog of CD4 that binds MHC class II (Liang et al., 2008), by T_{reg} cells may also be a mechanism through which these cells exert their influences. LAG-3 produced by T_{reg} cells has been demonstrated to suppress the maturation of antigen-presenting cells (Liang et al., 2008). T_{reg} cell expression of CD39 and CD73 may also prevent activation of antigen-presenting cells (Deaglio et al., 2007). These two surface molecules function together to break down extracellular ATP, which is released in large concentrations from damaged cells (Deaglio et al., 2007). Antigen-presenting cells can sense this extracellular ATP and undergo maturation and activation (Deaglio et al., 2007; Shevach, 2009). By breaking down this ATP, T_{reg} cells may be able to prevent activation of these antigen-presenting cells (Deaglio et al., 2007). Other mechanisms have also been suggested, such as secretion of fibrinogen-like protein 2 (fgl2), which may also depress the function of antigen-presenting cells, or surface expression of neuropilin-1 (Nrp-1), which may increase the strength of T_{reg} cell binding to antigen-presenting cells (Sarris et al., 2008; Shalev et al., 2008).

Finally, there is evidence to suggest that T_{reg} cells can prevent the activation of other cells by selective uptake of IL-2 (Chen et al., 2011; de la Rosa et al., 2004; Pandiyan et al., 2007).

Without IL-2, responder cells may never become activated, or they may become anergic or undergo apoptosis in the absence of costimulatory IL-2 (Chen et al., 2011; de la Rosa et al., 2004; Pandiyan et al., 2007). These potential mechanisms are summarized in Table 1.

Within the respiratory environment, most T_{reg} cell research has focused on the role of these cells in the suppression of asthma. Asthma is a chronic inflammatory disease that afflicts the airways, resulting in airway hyperreactivity and spontaneous airway obstruction (Lloyd & Hawrylowicz, 2009). It currently affects an estimated 300 million people worldwide, most of whom control the symptoms with glucocorticoid treatment (Lloyd & Hawrylowicz, 2009). Asthma is generally associated with a Th2 response, involving release of inflammatory mediators by T cells, mast cells and eosinophils (Lloyd & Hawrylowicz, 2009; Ray et al., 2010).

T_{reg} cells have long been implicated in the control of asthma, though the mechanisms through which they accomplish this control are still being studied (Lloyd & Hawrylowicz, 2009; McGuirk et al., 2010; Ray et al., 2010). Depletion of T_{reg} cells in murine models of asthma has been shown to greatly exacerbate symptoms (Lewkowich et al., 2005). This has been connected to a decrease in the Th1-promoting cytokine IL-12 and a concurrent increase in the Th2-associated cytokine IL-13 (Lewkowich et al., 2005). In addition, adoptive transfer of T_{reg} cells has been shown to prevent airway inflammation and hyperreactivity, or even to suppress symptoms when transferred after the onset of disease (Kearley et al., 2008).

Importantly, humans with mutations that impair T_{reg} cell function tend to have a higher incidence of asthma (Caudy et al., 2007; Lloyd & Hawrylowicz, 2009). Asthmatic children have been observed to have lower levels of T_{reg} cells in their lungs as compared with non-asthmatics (Hartl et al., 2007). Another study suggests that asthmatics have lower overall expression of FoxP3 compared to healthy donors (Lloyd & Hawrylowicz, 2009). Furthermore, glucocorticoid treatment has been shown to transiently increase T_{reg} cell numbers in asthmatic patients (Ryanna et al., 2009). A number of strategies have been proposed to increase T_{reg} cells in asthmatics, including isolation and *in vitro* expansion of T_{reg} cells, followed by their transfer back into the host (Ryanna et al., 2009). However, this would be an expensive and lengthy process. Thus, other therapies designed to promote *in vivo* T_{reg} cell expansion are currently being explored.

Recently, T_{reg} cells have also been shown to express toll-like receptors, and experiments have demonstrated that toll-like receptors have an impact on T_{reg} cell function (Dai et al., 2009; van Maren et al., 2008). However, depending on the type of toll-like receptor that is stimulated, T_{reg} cell function may be either enhanced or depressed (Dai et al., 2009; van Maren et al., 2008). This suggests, of course, that T_{reg} cells may have different responses to pathogens depending on the type of antigen encountered and the type of toll-like receptor signal that is received. Thus, the role of T_{reg} cells in different bacterial infections may vary widely depending on the nature of the bacteria. As such, the effect of T_{reg} cells in respiratory infections can be complex and difficult to predict.

4. Bacterial Respiratory Pathogens

4.1 Mycoplasma

As an infectious disease, mycoplasmas are probably the most under recognized pathogens known today. Often misconceived as a common cross-contaminant (Homburger &

Associated Protein/s	Potential Mechanism	Target Cell
Interleukin-10, TGF- β	Interference with T helper type 1 development and with secretion of proinflammatory cytokines	T cells, B cells, antigen-presenting cells (Bluestone & Abbas, 2003; Vignali et al., 2008; von Boehmer, 2005)
Interleukin-35	Unknown	Unknown (Chaturvedi et al., 2011; Collison et al., 2007; Collison et al., 2010)
Interferon- γ , Interleukin-17	Interference with T helper type 2 responses	Unknown
Galectin-1	Cell cycle arrest, inhibition of proinflammatory cytokine secretion, apoptosis	T cells, B cells (Garin et al., 2007; Shevach, 2009)
Perforin, Granzyme A, Granzyme B	Direct cytotoxicity	T cells, B cells, NK cells (Cao et al., 2007; Shevach, 2009)
Fas-FasL	Direct cytotoxicity, interference with antigen priming (dendritic cells)	B cells, CD8 T cells, Dendritic cells (Gorbachev & Fairchild, 2010; Strauss et al., 2009)
CTLA-4	Inhibition of antigen-presenting cell maturation, induced downregulation of CD80 and CD86 expression, blockade of CD80 and CD86	Antigen-presenting cells (Onishi et al., 2008; Shevach, 2009)
LAG-3	Inhibition of antigen-presenting cell maturation	Antigen-presenting cells (Liang et al., 2008)
CD39, CD73	Inhibition of antigen-presenting cell activation through breakdown of extracellular ATP	Antigen-presenting cells (Deaglio et al., 2007; Shevach, 2009)
Fgl2	Inhibition of antigen-presenting cells	Antigen-presenting cells (Sarris et al., 2008; Shalev et al., 2008)
Nrp-1	Strengthening of interaction with antigen-presenting cells	Antigen-presenting cells (Sarris et al., 2008; Shalev et al., 2008)
Interleukin-2	Uptake of exogenous interleukin-2, prevention of responder cell activation	T cells, B cells, Antigen-presenting cells (Chen et al., 2011; de la Rosa et al., 2004; Pandiyan et al., 2007)

Table 1. Mechanisms of Regulatory T Cell-Mediated Suppression

Thomann, 1994), mycoplasmas are in fact the etiological agent of a wide range of diseases in both animals and humans (Krause & Taylor-Robinson, 1992; Simecka et al., 1992). Because of their small size, mycoplasmas were first believed to be of viral origin. First isolated in 1898, *Mycoplasma mycoides* subsp. *mycoides*, was reported as the agent of contagious bovine pleuropneumonia in cattle (Nocard & Roux, 1990). Since, *Mycoplasma* species have been isolated from almost every domestic and laboratory animal.

Mycoplasma is commonly found as a respiratory pathogen. For example, *Mycoplasma pneumoniae*, the most common Mycoplasma in humans, causes up to 30% of all cases of community-acquired pneumonia. One study detected *M. pneumoniae* in over half of children above the age of five. This would make Mycoplasma the single most common pathogen in humans. While most cases of Mycoplasma infection are not life threatening, some do require hospitalization (more than 100,000 people per year). Mycoplasmas have also been suggested to have a role in the exacerbation of chronic asthma and certain autoimmune conditions (Atkinson et al., 2008; Dobbs et al., 2010; Woolard et al., 2004).

There exists an interesting interplay between Mycoplasma and the host immune response. Most of the information in this regard is due to studies using the natural murine pathogen *Mycoplasma pulmonis*, which causes acute and chronic diseases of the respiratory tract in rats and mice (Hardy et al., 2002). Several studies demonstrated that immune responses against mycoplasma can be immunopathologic, contributing to disease severity. However, immune responses are also important in restricting infection to the lungs, preventing dissemination to other sites. Severe combined immunodeficient mice (T and B cell deficient) and athymic mice (T cell-deficient) develop less severe pulmonary lesions due to *M. pulmonis* infection than similarly infected wild type mice (Evengard et al., 1994; Keystone et al., 1980). Adoptive transfer of lymphocytes into severe combined immunodeficient mice prior to *M. pulmonis* infection restored the level of mycoplasma disease (Cartner et al., 1998). Importantly, no difference in lung colony forming units was observed in these studies, providing further evidence that the development of disease is due to immunopathologic immune responses. Depletion of T cells from hamsters showed a similar reduction in lesions after infection with *M. pneumoniae* (Taylor et al., 1974). Studies utilizing *M. pulmonis* have shown that disease severity is directly related to Th cells. Depletion of these cells prior to infection led to significant decreases in disease severity, as measured by weight loss and lesion incidence (Jones et al., 2002). Since Th cell responses can be separated into Th1 or Th2 lineages, further studies were performed using IFN- γ -deficient mice and IL-4-deficient mice. Mice lacking IFN- γ (which preferentially mounted a Th2 cell response) developed more severe disease upon infection with *Mycoplasma pulmonis* at an early time point (Woolard et al., 2004). In contrast, mice lacking IL-4 (which preferentially mounted a Th1 cell response) did not demonstrate any exacerbation of disease (Woolard et al., 2004). Furthermore, immunization with mycoplasma antigen results in resistance to infection in IL-4-deficient mice, but not IFN- γ -deficient mice (Bodhankar et al., 2010). Overall, these studies suggest that Th2 responses contribute to mycoplasma-associated immunopathology, while Th1 responses promote resistance to infection.

CD8⁺ cytotoxic T cells also play a role in mycoplasma disease, though their role may be regulatory in nature. When CD8⁺ T cells were depleted from mice prior to infection with *M. pulmonis*, disease severity increased (Jones et al., 2002). Similar results were observed in studies involving rats. F344 rats developed less severe disease after infection with *M. pulmonis* as compared to LEW rats (Davis & Cassell, 1982; Davis et al., 1982, 1985). This was connected to higher levels of CD8⁺ T cells in the lungs and draining lymph nodes of F344 rats compared to LEW rats. This effect may be due to the secretion of IFN- γ by CD8⁺ T cells, which could dampen immunopathologic Th2 cell responses.

Recent studies from our lab showed that T_{reg} cells clearly control the severity of disease in mycoplasma respiratory infection. Depletion of T_{reg} cells using anti-CD25 antibody prior to

infection with *M. pulmonis* resulted in significant increases in clinical disease severity. The T_{reg} cell-depleted mice lost significantly more weight over the course of the study and displayed a significantly higher incidence of gross lung lesions. In addition, T_{reg} cell-depleted mice had more severe histological lung lesions, which included increased peribronchial infiltration of inflammatory cells, airway exudate, epithelial hyperplasia, and alveolitis. This effect was clearly related to a decrease in the level of T_{reg} cells, as the anti-CD25 antibody was shown to specifically deplete CD4⁺CD25⁺FoxP3⁺ cells without affecting other cell populations. Increased disease in T_{reg} cell-depleted mice was also concurrent not only with increases in lung cell infiltration but also with increases in the levels of mycoplasma-specific serum antibodies. Significantly, depletion of T_{reg} cells had no effect on mycoplasma numbers (Odeh & Simecka, in preparation). Thus, T_{reg} cells dampen the severity of inflammatory disease due to mycoplasma respiratory infection most likely through regulation of immune responses, in an apparent attempt to limit damage within the lung, but T_{reg} cell activity does not contribute to persistence of mycoplasma infections, in contrast to other studies such as those discussed above with Leishmania infection.

The mechanisms of how T_{reg} cells regulate the development of inflammatory lesions is under investigation, but our results suggest that it is a result of activities of a novel population of T_{reg} cells. Our studies demonstrated that there was an increase in total cell numbers in the lung of infected mice after T_{reg} cell depletion, with almost all populations being affected. Most interestingly, there was a preferential increase in the percentage of IL-13⁺ cells in the lower respiratory lymph nodes due to T_{reg} cell depletion prior to infection, suggesting T_{reg} cells suppressed Th2 cell responses and perhaps promoted Th1 cell responses. Interestingly, there were increases in T_{reg} cells in lower respiratory tract lymph nodes during mycoplasma disease pathogenesis, but neither IL-10 nor TGF- β production by these T_{reg} cells in response to mycoplasma could be demonstrated. Further characterization found that these T_{reg} cells included two subpopulations that expressed either intracellular IFN- γ or IL-17, suggesting that mycoplasma-specific T_{reg} cells may act through novel mechanisms. In fact, *in vitro* cultures containing T_{reg} cells and Th cells from infected mice secreted significantly higher levels of IFN- γ and IL-17 when stimulated with mycoplasma antigen as compared to Th cells alone. These data provided evidence that T_{reg} cells might stimulate the secretion of IFN- γ and IL-17 cytokines by Th cells. In support, depletion of T_{reg} cells from infected mice led to a decrease in the *in vivo* secretion of IFN- γ and IL-17 by T helper cells (Odeh & Simecka, in preparation). These data suggest that two unique populations of T_{reg} cells, IFN- γ ⁺ or IL-17⁺, develop in mycoplasma-infected mice, and that these novel populations of T_{reg} cells participate in control of the disease. Furthermore, these data suggest that IFN- γ ⁺ and IL-17⁺ T_{reg} cells promote the secretion of these cytokines by Th cells. Thus, the activation of this unique population of T_{reg} cells in mycoplasma infections may be beneficial, as the stimulation of IFN- γ and IL-17 production by Th cells would suppress the development of immunopathologic Th2 cell responses.

4.2 Mycobacterium

Current estimates are that one-third of the world population is infected with *Mycobacterium tuberculosis* (Bloom & Small, 1998; Dai et al., 2009; Urdahl et al., 2011). *M. tuberculosis* is responsible for 1.7 million deaths worldwide each year, though most of these deaths occur in developing countries, and/or in immunocompromised individuals (Kwan & Ernst, 2011;

Lawn & Zumla, 2011). The pathogenesis of tuberculosis is interesting. The disease is characterized by the persistence of infection and the formation of granulomas by the host to prevent the spread of the infection. Upon initial exposure, mycobacteria are phagocytosed by alveolar macrophages (Redford et al., 2011). However, through mechanisms that involve altered production of reactive nitrogen intermediates and prevention of phagosome maturation, *M. tuberculosis* bacteria are able to survive within the host cells (Flynn & Chan, 2003; Redford et al., 2011). The persistence of Mycobacteria leads to granuloma formation, which not only prevents spread of the infection, but also benefits the bacteria by masking them from the immune response (Flynn & Chan, 2003). This results in a latent infection that never progresses to symptomatic tuberculosis (Flynn & Chan, 2003). Studies have demonstrated that control of tuberculosis is dependent on IL-12 and Th1 cell responses (Altare et al., 1998; Newport et al., 2003; Redford et al., 2011; Urdahl et al., 2011). Th1 cell responses are critical in macrophage activation and the formation and maintenance of the granuloma (Saunders & Britton, 2007). Thus, like Mycoplasma and other infectious diseases, the host response to *M. tuberculosis* infection is critical in determining the extent of lesions and outcome of infection, and, in the case of *M. tuberculosis*, impairment of Th1 responses against the pathogen leads to spread of infection and more severe disease.

A small percentage of infected individuals, for reasons that are still not well understood, will develop symptoms, which include fever, cough, chest pain, and night sweats (Bark et al., 2011; Redford et al., 2011), but this is likely linked to a breakdown in Th1 responses meant to isolate the infection. One of the common findings in individuals with symptomatic tuberculosis, either from primary exposure or from reactivation of latent infection, is a high concentration of IL-10 in the blood (Boussiotis et al., 2000; Redford et al., 2011). In support of a critical role for IL-10 production in the pathogenesis of tuberculosis, IL-10 production was associated with the reactivation of tuberculosis in a mouse model of this disease (Turner et al., 2002). IL-10 can dampen macrophage activation and help stimulate the development of Th2 cell responses and alternatively activated macrophages (Kahnert et al., 2006). Taken together, IL-10 production in patients with active tuberculosis likely impairs the development or maintenance of a Th1 proinflammatory response, leading to a breakdown of the granulomas that are critical in limiting the spread of infection and damage to the host.

Since populations of T_{reg} cells are often a source of IL-10, studies were performed examining the role of T_{reg} cells in *M. tuberculosis* respiratory infection. T_{reg} cells in mice were indeed found to proliferate in response to mycobacteria infection (Shafiani et al., 2010) and were observed to localize to sites of Th cell responses in the lungs (Kahnert et al., 2006). By adoptively transferring *M. tuberculosis* specific T_{reg} cells, it was found that T_{reg} cells delayed the infiltration of effector T cells into the lung environment, and led to higher bacterial counts in the lungs of recipient mice (Shafiani et al., 2010). This delay in cell infiltration due to T_{reg} cells likely impaired host responses that effectively control mycobacteria infection, disrupting protective granuloma formation. In fact, depletion of T_{reg} cells results in higher numbers of mycobacteria (Kahnert et al., 2006). Thus, the production of T_{reg} cell responses in tuberculosis can impair host resistance to infection, and in fact, the overactivity of T_{reg} cells could participate in the transition of quiescent forms of tuberculosis to active disease. This represents a case where the attempt of T_{reg} cells to dampen inflammatory responses may actually have a negative effect on disease outcome.

4.3 Bordetella

Bordetella pertussis is the bacterium responsible for whooping cough, a disease that can afflict all age groups, but which is especially predominant and dangerous in children (Dunne et al., 2009; Marzouqi et al., 2010). In addition to the cough itself, other symptoms can include fever, nausea, convulsions, pneumonia, and, in severe cases, encephalopathy (Marzouqi et al., 2010). Even with the use of pertussis vaccines, the incidence of Bordetella infections is very high, with 40-50 million cases reported worldwide each year (Marzouqi et al., 2010). Of these, 300,000-400,000 result in death, mostly in children living in developing countries (Marzouqi et al., 2010). This makes whooping cough the most common vaccine-preventable disease in the world (Marzouqi et al., 2010).

Upon initial exposure, *B. pertussis* adheres to the mucosal epithelium along the respiratory tract (de Gouw et al., 2011). It can then form a protective biofilm that allows it to mask itself from immune cells (de Gouw et al., 2011). There is even evidence that certain strains of Bordetella can invade host cells, thus avoiding many host responses (de Gouw et al., 2011). To promote its longevity and survival within the host, *B. pertussis* produces a number of toxins and virulence factors (de Gouw et al., 2011). It is well established at this point that clearance of Bordetella from the host requires a Th1 response, mediated by IFN- γ (de Gouw et al., 2011). Experiments with vaccines have shown that augmentation of the IFN- γ -mediated Th1 cell response leads to increased clearance of Bordetella (Marzouqi et al., 2010). To interfere with this, Bordetella can induce the production of IL-10, and, most interestingly, can stimulate the proliferation of IL-10-producing T_{reg} cells (de Gouw et al., 2011; Higgins et al., 2003). T_{reg} cells and IL-10 production can then dampen the Th1 cell response against the pathogen, delaying clearance of the organism and increasing its chances of transmission to another host (de Gouw et al., 2011). In mice depleted of T_{reg} cells, there was an increase in the infiltration of immune cells into the lung environment (Higgins et al., 2003). This corresponded with a significant increase in the incidence of lung lesions, indicating a strong inflammatory response against the infection (Higgins et al., 2003). Thus, it appears that *B. pertussis* harnesses the host's own mechanisms to modulate inflammatory responses by stimulating T_{reg} cells to dampen these responses, thus preventing efficient elimination of the pathogen.

However, the role of T_{reg} cells in Bordetella infections is more complex. The cascade of events through which *B. pertussis* stimulates T_{reg} cell activity is mediated by toll-like receptors. Studies demonstrated that Bordetella infection results in the production of IL-10 by dendritic cells (Higgins et al., 2003). The stimulation of dendritic cells to produce IL-10 is driven by engagement of toll-like receptor 4 (TLR4). The IL-10 released by Bordetella-stimulated dendritic cells, in turn, helps to promote the expansion of the IL-10-secreting T_{reg} cell population (Higgins et al., 2003). This is supported by studies showing that *B. pertussis* infection of TLR4-deficient mice results in a significantly lower number of antigen-specific T_{reg} cells than is found in wild-type mice. Furthermore, there was a concurrent decrease in the IL-10 levels (Higgins et al., 2003). The absence of IL-10-secreting T_{reg} cells resulted in an increase in the infiltration of immune cells into the lung environment (Higgins et al., 2003). This corresponded with a significant increase in the incidence of lung lesions, indicating a strong immunopathologic response (Higgins et al., 2003). Thus, *B. pertussis* utilizes a pathway mediated by TLR4 recognition of the organisms to stimulate T_{reg} cell-mediated

suppression of inflammatory responses that prevents both efficient clearance of the organism and damaging immunopathologic responses.

4.4 Chlamydia and streptococcus

There has been little additional work done on the role of T_{reg} cells in other types of respiratory infections. However, there are some interesting studies on Chlamydia and Streptococcus respiratory infections that suggest an important role for T_{reg} cells in these diseases.

Chlamydia muridarum is a murine pathogen that causes disease similar to that of *Chlamydia trachomatis* in humans (Carey et al., 2011). As such, it is commonly used as a murine model. Normally, *C. trachomatis* manifests in humans as a sexually-transmitted disease, infecting the genital tract (Carey et al., 2011). However, it can infect other sites as well, including the respiratory tract, and, as a result, experiments have been performed using experimental *C. muridarum* lung infections (He et al., 2011). TLR2-deficient mice infected intranasally with *C. muridarum* developed more severe lung inflammation and more severe overall disease as compared to chlamydia-infected wild type mice (He et al., 2011). This was associated with an increase in the concentrations of the proinflammatory cytokines IFN- γ , IL-12, and IL-17, and a concurrent increase in the infiltration of immune cells in lung tissue (He et al., 2011). However, the lack of TLR2 had no effect on the clearance of the organism, as no differences in bacterial counts were found between wild type mice and TLR2-deficient mice (He et al., 2011). Recently, engagement of TLR2 was shown to promote the development of T_{reg} cells (Chen et al., 2009). Thus, it has been theorized that the increased immunopathology in *C. muridarum*-infected, TLR2-deficient mice may be due to a deficiency of T_{reg} cells, though this has not yet been conclusively demonstrated (He et al., 2011). If so, the TLR-mediated mechanisms involved in promoting T_{reg} cell activity by *C. muridarum* infection may be similar to those described above for Bordetella, and this could be a common approach through which some bacteria harness the immunosuppressive activity of T_{reg} cells.

One of the most common respiratory bacteria, and the one most often responsible for severe cases of pneumonia, is *Streptococcus pneumoniae* (Jones et al., 2010). Despite its role as the quintessential pneumococcal pathogen, very little work has been performed in the area of *S. pneumoniae* and T_{reg} cells. In studies that examined the role of Streptococcus in asthma and airway hyperreactivity, it was shown that both intact *S. pneumoniae* and pneumococcal proteins can induce the development of T_{reg} cells (Preston et al., 2011; Thorburn et al., 2010). The role of T_{reg} cells in pneumococcal disease is unclear, but recent studies have begun examining the role of T_{reg} cells in the generation of humoral immune responses against *S. pneumoniae*. Mice were treated with T_{reg} cell-depleting antibodies and infected with live streptococcus. These mice develop similar levels of antibody responses as those in normal mice with intact T_{reg} cell activity (Lee et al., 2005). Similar results were obtained when mice were given heat-killed streptococcus or protein-polysaccharide conjugates (which are used in *S. pneumoniae* vaccines) (Lee et al., 2005). Thus, it appears that T_{reg} cells do not play a role in the development of anti-streptococcal humoral immunity. Further studies are needed to determine whether T_{reg} cells play a role in disease pathogenesis or modulating protective immunity against *S. pneumoniae*. However, the data do suggest that other bacterial species can promote the development of T_{reg} cell responses, which may play variable levels of importance depending upon the bacteria, the host, and the infection.

5. Conclusion

As discussed above, there has been limited work examining the role of T_{reg} cells in the pathogenesis of bacterial lung diseases. It is clear that modulation of T_{reg} cell activity is done in some cases to benefit the host and in other cases benefitting the pathogen. Because the lung is a critical organ and a common site for exposure to infection, T_{reg} cell activity is probably most important in dampening inflammatory responses to infections in order to minimize damage to the lung tissue. As indicated earlier, there are multiple mechanisms through which T_{reg} cells modulate these inflammatory responses and lesions. Although one of the most common mechanisms is through the production of the anti-inflammatory cytokine IL-10, T_{reg} cells, as shown in *Mycoplasma pneumoniae*, may also prevent the development of potentially damaging immune responses by promoting other types of immunity. Interestingly, some respiratory pathogens, as well as other bacteria, have devised mechanisms to promote T_{reg} cell development in an apparent attempt to interfere with host resistance and delay their clearance. Thus, T_{reg} cells likely have varied activities in pulmonary bacterial diseases, which are probably host and bacterial species specific.

Research on T_{reg} cells and bacterial infections may also benefit treatment of other respiratory diseases. In recent years, a large amount of research has examined the role of T_{reg} cells in asthma and other allergic diseases. Specifically, research indicates that stimulating the development and activation of regulatory T cells may suppress allergic reactions and asthma (Ray et al., 2010). Suggested methods for how to stimulate the development of T_{reg} cell responses vary. Interestingly, one possible approach involves treatment of patients with bacteria or bacterial products (Fonseca & Kline, 2009; Trujillo & Erb, 2003), and indeed, there are cases in which this type of therapy has been experimentally validated (Crother et al., 2011; Preston et al., 2011; Thorburn et al., 2010). This promising approach may have a broader utility since, as discussed in this article, different kinds of bacteria appear to be able to elicit different types of T_{reg} cell responses. This suggests that further studies into how bacteria activate T_{reg} cells are merited and could result in novel approaches to selectively and appropriately activate T_{reg} cells in the treatment of certain human diseases.

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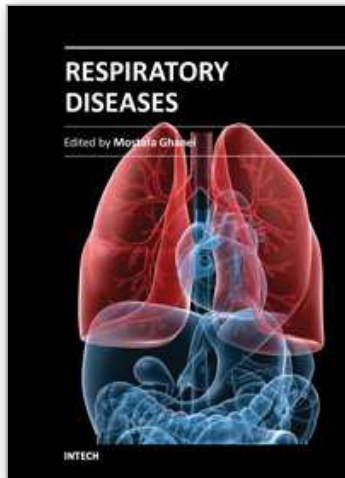
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