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THE MULTIFACETED ROLE OF T CELL-MEDIATED IMMUNITY IN PATHOGENESIS AND RESISTANCE TO MYCOPLASMA RESPIRATORY DISEASE

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Abstract

Mycoplasma respiratory diseases have a significant impact on the economy, health and wildlife. The hallmark of these diseases is the persistence of the mycoplasma infections and chronic inflammatory responses associated with the airways. There is still much that needs to be understood about the immune mechanisms involved in mycoplasma disease and resistance from infection. It is clear that immune responses can contribute to the generation of inflammatory lesions in mycoplasma respiratory disease, as well as provide protection from infection and extrapulmonary dissemination of the organisms. The evolution of this lung disease is under the control innate immune mechanisms and the contrasting effects of different T cell populations. The mechanisms of immunity involved in mycoplasma diseases are multifaceted, and a fascinating story of its complexity is being uncovered. Research in mycoplasma respiratory diseases have underscored the idea that immunity along the respiratory tract against infectious agents is a dynamic process and involves a network of cellular and cytokine signals that determine the type of responses generated, and ultimately, the outcome of infection. The aim of this article is to present on overview of our work on mycoplasma disease and immunity, focusing on the interactions and regulation of T cell responses that influence disease pathogenesis. We will first provide an overview of immune mechanisms involved in controlling infection and participate in the generation of T cell responses, and the role of T cell populations in generating protection and contributing to lesion development will be discussed.

Keywords

Mycoplasma disease; immunity; T cells

INTRODUCTION

As an infectious disease, mycoplasmas are probably the most under recognized pathogens known today. These bacteria have unusually small genomes and are known to infect and colonize mucosal surfaces such as those along the respiratory and urogenital tracts. Belonging to the class *Mollicutes*, meaning “soft skin”, they differ from other bacteria in that they lack a cell wall, rendering them resistant to certain antibiotics. First isolated in 1898, *Mycoplasma mycoides* subsp. *mycoides* was reported as the causative agent of contagious bovine pleuropneumonia in cattle [1]. Since then, mycoplasmas are found to be the etiological agents of a wide range of diseases in both animals and humans [2–3].

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Mycoplasmas are excellent examples of respiratory pathogens that infect a wide variety of hosts including reptiles, cattle, pigs, chickens, dogs and rodents, as well as humans. The most recognized human pathogen is *Mycoplasma pneumoniae*, the leading cause of respiratory related illness worldwide, which is responsible for the respiratory disease "walking pneumonia." This disease is a community-acquired pneumonia affecting students who inhabit dormitories, military personnel in military barracks and attendees at summer camps [4–6]. The Center for Disease Control estimates that *M. pneumoniae* causes 2 million cases of pneumonia per year and about 100,000 of those results in the hospitalization of patients. To complicate matters, *M. pneumoniae* is also implicated in the exacerbation of other respiratory conditions such as asthmatic airway hypersensitivity reactions, chronic obstructive pulmonary disease (COPD) and cystic fibrosis [7–13]. While many of these cases of pneumonia are acute, some result in chronic infections in which can lead to the development of immunopathology. Because of their prevalence, mycoplasmas have a profound economic impact not only health care and biomedical research but also on agriculture as an infectious agent of cattle, swine, sheep and other livestock [2]. A hallmark of these infections is the persistence of the organism despite the presence of immune response.

The reasons that mycoplasma infections can persist are not entirely clear. It is clear that host immune responses against mycoplasma are complex and ultimately determine resistance to infection, severity of disease and spread of infection in the body. Although immunity is known to prevent or control infections, immune responses can also promote the development of inflammatory lesions associated with mycoplasma disease. T cells are critical in the regulation of general immunity, and have a critical impact on the progression of mycoplasma disease. In this review, we will highlight the multifaceted roles of T lymphocytes in pathogenesis of and resistance to animal and human mycoplasma disease, as well as some of the factors that regulate the type of T cell responses generated. Throughout this chapter, we will present and reference previous, and in many cases ongoing studies related to these topics. Although this review is focused on our studies with mycoplasma respiratory disease, the principles described will likely be true for mycoplasma diseases at other tissue sites.

The Complexity of Immune Interactions with Mycoplasma

Disease pathogenesis of mycoplasmas is influenced by a multitude of factors, providing a complex picture of subtle host-parasite interactions that result in either control of infection or development of disease. We have focused much of our work on the immune responses against *Mycoplasma pulmonis. M. pulmonis* is a natural pathogen that causes respiratory disease in rodents, and murine infections with this mycoplasma serve as an excellent model for studying the host immune and inflammatory responses during acute and chronic mycoplasma respiratory disease, including those of human and other animals. As with many mycoplasma diseases, a major determinant in disease progression of *M. pulmonis* infection is the host genetic background [14–16]. For example, different strains of mice have a different immune response against infection *M. pulmonis*. Early studies demonstrated that C57BL/6 mice are more resistant to mycoplasma infections -*than other mouse strains. Mycoplasma disease in C57BL/6 mice results in an acute infection with little to no lesion damage and quick clearance of the microorganism [17–19]. However, C3H/HeN and Balb/c mice are susceptible to mycoplasma infections resulting in a chronic disease state demonstrating increased clinical disease and pulmonary tissue damage, which will eventually result in death [17–19]. The chronic disease state in these susceptible mice strains is identified by increased weight loss, matted or ruffled fur indicating fever, and malaise. As increased clinical disease is observed pulmonary immunopathology begins to develop and is identified by the development of gross lesions characterized by neutrophilic exudates in the

airway lumina, hyperplasia of airway epithelium, peri-bronchial and peri-vascular lymphoid hyperplasia/infiltration, and mixed neutrophilic and histiocytic exudates in the alveoli. Further studies demonstrate that inbred strains of mice display a continuum from resistant to severe disease after infection with *M. pulmonis* [19] demonstrating that host susceptibility or resistance to mycoplasma infection is under multigenic control. These genetic differences are likely linked to components of the immune system, as differences in disease susceptibility correspond with the types and intensity of immunity generated [18-20-24]. In addition, gender of the host can also contribute to the extent of disease. Our studies found that male mice develop more severe alveolar pneumonia after *M. pulmonis* infection than female mice, regardless of the mouse strain [25]. Similar findings are observed in the human mycoplasma disease, *M. pneumoniae* [26–28]. Despite the vast amount of information regarding mycoplasmas, there is still much to understand about the factors that influence mycoplasma disease pathogenesis, including the impact of host responses on disease.

Immunologic responses probably have the greatest impact on the progression of mycoplasma respiratory disease. One of the most consistent characteristics of most mycoplasma respiratory diseases, including disease caused by *M. pulmonis* and *M. pneumoniae*, is the large accumulation of lymphoid cells along the respiratory tract [2-3-29]. Both T and B cells accumulate in the lung of *M. bovis* respiratory disease in calves, which is similar to the findings of both human and murine mycoplasma respiratory disease [30]. Lymphoid infiltration suggests that lymphocyte activation and recruitment are key events in the progression of mycoplasma inflammatory disease. The role of lymphoid responses in the development of other chronic inflammatory diseases is well documented, and lymphocyte activation is similarly important in mycoplasma respiratory disease. The best evidence for immunopathologic responses in mycoplasma respiratory diseases comes from studies using immunocompromised animals. T cell-depleted hamsters develop less severe *M. pneumoniae* disease [31]. Likewise, *M. pulmonis* infection of *s*evere *c*ombined *i*mmuno*d*eficient (SCID) mice (lack functional B or T cells) or athymic mice (T cell deficient) results in reduced pulmonary lesions as compared to immunocompetent counterparts [32–33]. Furthermore, we found that reconstitution of SCID mice with lymphocytes restores mycoplasma disease severity. The differences in disease severity were not due to altered clearance of organisms within the lung as mycoplasma numbers do not differ between immunocompetent or SCID mice [34]. Clearly, adaptive immune responses contribute to disease severity by promoting inflammatory responses, independent of the level of infection.

Although adaptive immunity contributes to disease pathology [18–22], these responses localize the infection to the lung, preventing the spread of mycoplasma to other tissues of the body. Disseminated mycoplasma disease is common in immunodeficient animals and humans. Hypogammaglobulinemic humans are more susceptible to complications (e.g., polyarthritis and meningitis) due to *M. pneumoniae* [35–36]. Unlike their murine immunocompetent counterparts, the immunodeficient mice [32–34] are unable to control dissemination of the microorganism from the lungs into the rest of the body. This leads to colonization of adjacent organs such as the spleen and liver as well as invasion into the joints leading to the development of arthritis [32–34]. Ultimately, left untreated these mice would be unable to sufficiently clear the pathogens and death would result. However, susceptible immunocompetent mice, although suffering from an exacerbated inflammatory response resulting in lesion damage, are able to contain the microorganisms at the site of infection in the lungs. We further demonstrated that passive transfer of antibody prevents arthritis from developing in *M. pulmonis*-infected immunodeficient mice [34]. Thus, lymphoid, particularly antibody, responses are important in localizing mycoplasma infections to mucosal sites of infection, preventing the spread to other tissues and the development of arthritis.

Despite having a limited effect on clearance of an established mycoplasma infection and contribution to disease pathology [18–22], immunity can play a role in resistance to mycoplasma infection and subsequent disease. Immunization against mycoplasma disease is possible [37–45]. However, protective immune responses are variable and often provide only short-lived resistance [46–47]. Furthermore, immunization with organisms are easily isolated from challenged animals may only confer partial protection from infection, as found in studies using *Mycoplasma bovis, Mycoplasma hyopneumoniae* and *M. pulmonis* [43-48-50]. However, our laboratory has demonstrated that local responses along the respiratory tract are more effective against mycoplasma infection than those generated after systemic immunization [51]. Nasal and pulmonary immunization can be effective [51–52], but we have shown that the immune responses in the upper and lower respiratory tracts differ [53–54], which may indicate variability in effective immune mechanisms. Interestingly, there are instances when vaccination may result in exacerbation of disease, rather than protection. For example, immunized guinea pigs can develop more intense inflammatory responses after *M. pneumoniae* infection, indicating generation of immunopathologic, rather than protective, responses [55]. Thus, protective immunity can be generated, but the balance between the beneficial and harmful immune responses ultimately determines the outcome of immunization against mycoplasma infection.

Overall, the hallmark of many mycoplasma diseases is the persistence of the organism, with frustrated and unproductive immune responses leading to chronic inflammatory disease. It is the balance between contrasting immune responses, those that are beneficial in controlling or preventing infection and those that contribute to the severity of disease of immune responses, which often determines the outcome of mycoplasma infections. Because of this complexity, the delineation of immune mechanisms involved in mycoplasma disease can be overwhelming. One approach to illuminate these mechanisms is to focus on the central effector and regulatory cells of the immune system, the T lymphocytes. Once understood, the interactions of T cells with the other components of the host response should begin the disentanglement of the interactions between mycoplasma and the immune system.

TLymphocytes populations and immunity

The T cell, in many cases, is likely to determine the nature of host responses generated against mycoplasma, and these responses subsequently determine the outcome of infection. T cells are critical in the resistance to almost every other infectious agent, but T cells can also contribute to host immune-mediated inflammatory responses that are important in disease pathogenesis. Interaction with both the innate and adaptive arms of the immune system demonstrates T cell capabilities to be either regulatory or effector cells in response to infection. Activation of T cells begins with antigen presenting cells (e.g. macrophages, dendritic cells, B cells) displaying peptides from pathogens or their products to T cells, which express receptors specific for these antigens. Once activated, T cells influence all arms of immunity. The release of T cell factors initiate and modulate the activity of inflammatory cell populations and participate in inducing and maintaining acquired immunity and generating memory lymphocyte populations. T cells can fine-tune the humoral immunity by determining the class of and influencing the specificity of antibody responses. Overall, the tremendous potential in T cell activity makes delineation of the role of this lymphocyte population in disease very complex, but of fundamental importance.

T cells are divided into two major basic groups differentiated by the expression of cell surface receptors and their effector functions. T helper cells (Th) express the co-receptor CD4, while CD8 is found on the surface of cytotoxic T lymphocytes (CTLs). T helper cells are further divided into more complex groups defined mostly by the cytokines produced. The current classifications of these $CD4^+$ Th cell groups include Th1, Th2, Th17 and T regulatory (T_{reg}) cells. Each of these Th cell subsets has defined but somewhat overlapping

roles in host immunity. Th1 cells secrete interferon-gamma (IFN-γ), interleukin-2 (IL-2), tumor necrosis factor beta (TNF-β also known as lymphotoxin) and granulocyte macrophage-colony stimulating factor (GM-CSF) [56–57]. The secretion of these cytokines amplifies the host immune response to intracellular bacteria and viruses making this immune response better at mediating cellular immunity. Th1 cells can also contribute to the development of inflammatory responses and can shape antibody responses to foster killing of some extracellular pathogens. Th2 cells are most effective as mediators of the humoral immune responses and are characterized by the secretion of IL-4, IL-5, IL-9, and IL-13 [56–58]. These cytokines promote antibody class switching by B cells as well as differentiation of B cells into antibody secreting plasma cells. IL-4, for example, can help initiate B cell activation and can also promote immunoglobulin class switching to immunoglobulin E (IgE). IgE, along with IL-5, is most effective against extracellular parasites and assists in eosinophil and mast cell degranulation. Th17 cells secrete IL-17, IL-17F, IL-6 and IL-22 [59]. Secretion of these cytokines assists in the induction of inflammation and activation of neutrophils to combat extracellular bacteria. T_{reg} cells are a special group of effector T cells that have the ability to suppress the inflammatory response through either contact dependent mechanisms such as Fas/FasL interactions or through secretion of the cytokines IL-10 and transforming growth factor-beta (TGF-β), known to suppress T cell functions and induce tolerance to antigens [58]. T_{reg} cells can also help dampen inflammatory responses by inhibiting the maturation of dendritic cells, which in turn leads to reduced T cell activation.

The cytokines secreted and surface molecules expressed by these effector Th cell subsets define their functional capabilities, and sometimes these responses are beneficial to the host. In some situations, these Th cell subsets may exacerbate autoimmune reactions, allergies, asthma, infectious disease states, such as inflammatory reactions or may promote chronic infections. For example, Th1 responses are beneficial to control many intracellular pathogens and fungi infections, but they could also exacerbate autoimmune diseases such as psoriasis, multiple sclerosis and rheumatoid arthritis [60–64]. Similarly, Th2 cell activation can control or eliminate extracellular pathogens such as *Borrelia burgdorferi* and helminthes, but these responses can worsen some viral infections, allergic responses, asthma and airway hypersensitivity reactions [65–72]. Th17 effector cells are important in an effective immune defense of infections caused by *Klebsiella pneumoniae, Bacteroides fragilis, Candida albicans*, as well as *Mycobacterium tuberculosis* [73–75]. However, this subset of T cells is also implicated in the exacerbation of autoimmune diseases such as rheumatoid arthritis [76–77]. IL-10, a product of T_{reg} and other cells types, can contribute to persistence of some infections through the dampening of the host responses capable of combating infection [78–84]. Thus, the control of Th cell subset differentiation and their subsequent activation can ultimately determine the outcome of infections.

$CD8^+$ T lymphocytes also contribute to host immune responses against infections. Their major functions include the killing of bacterially- or virally-infected cells, as well as cancer cells. Cytolytic activity is mediated through the release of perforin, granzyme B and other factors or the interaction between FasL and Fas on the surface of CTL and target cells. In both cases, apoptosis of the target cell occurs. Although killing of cells is a major function of CTL, $CD8^+$ T cells can also produce substances, e.g. granulysin, that directly kill intracellular bacteria [85], suggesting $CD8^+$ T cells may also mediate killing of intracellular pathogens. In addition, $CD8^+$ T cells can secrete IFN-g and other cytokines that can also modulate immune and inflammatory responses against infectious agents, such as activation of NK cells or macrophages. Interestingly, $CD8^+$ T cells were once referred to as T suppressor cells, because of their ability to dampen immune responses, particularly those mediated by Th cells [86]. Thus, $CD8^+$ T cells could play a number of roles in the generation of immunity and pathogenesis of infectious disease.

T Cell Populations and Their Role in Mycoplasma Respiratory Disease

It is clear that lymphocyte recruitment and activation are important in the pathogenesis of mycoplasma respiratory disease, and T cells are an important component of these responses. As indicated earlier, a common characteristic of most animal and human mycoplasma diseases is an accumulation of lymphoid cells in lungs consistent with chronic inflammation [3-29-87-88]. We found predominant increases in T cell numbers occur in both lungs and draining (hilar and mediastinal) lymph nodes of the lower respiratory tract [89]. Increases in the major T cell populations, Th and $CD8^+$ T cells, occurred between 7 to 14 days after *M. pulmonis* infection corresponding with lesion development. Importantly, $CD4^+$ T cells were the major population of T cells in the lungs of mice 14 days after infection. To explore the roles that $CD4^+$ and $CD8^+$ cells play in disease pathogenesis, mice were given specific antibodies to deplete 98% of their $CD4^+$ or $CD8^+$ T cells three days before infection with *M. pulmonis* and every five days following the infection. Depletion of the $CD8^+$ T cell subsets in mice revealed increased lesion severity and increased signs of clinical illness, including a significant increase in weight loss as compared to $CD4^+$ depleted or mixed $CD4^+$ and $CD8^+$ depleted groups. In contrast, depletion of $CD4^+$ T cells decreased lesion severity and clinical illness. Interestingly, the numbers of mycoplasma colony forming units (CFUs) recovered from the lungs of the control mice and all depleted mice did not differ, signifying that depletion of the T cell subsets did not impact the clearance of the microorganism from the lungs. Thus, a population of $CD4^+$ Th cells contributes to the immunopathology associated with *M. pulmonis* pulmonary disease, whereas $CD8^+$ T cells dampen these inflammatory responses.

A recent study from our lab demonstrates that $CD4^+$ Th cells, but not $CD8^+$ T cells, contribute to the resistance to mycoplasma infection in nasal-pulmonary immunized mice [90]. As expected, *in vivo* depletion of $CD4^+$ T cells prior to nasal pulmonary immunization of mice with mycoplasma antigen resulted in elimination of any indication of immune mediated resistance to *M. pulmonis* infection. Depletion of $CD8^+$ cells had no effect on resistance. These data demonstrate that $CD4^+$ T cells are critical in the induction of mycoplasma-specific immune responses involved in resistance to mycoplasma infection. In additional studies, immunized mice were depleted of Th cells prior to infection with *M. pulmonis* and three days later, there was no reduction in the numbers of mycoplasma in the Th cell depleted, immunized mice, indicating that Th cells are directly involved in effector mechanisms against mycoplasma infection. To further examine this possibility, adoptive transfer of $CD4^+$ T cells isolated from the lungs of immunized mice resulted in a logarithmic reduction of mycoplasma numbers recovered from the lungs of infected mice as compared to those mycoplasma numbers recovered from lungs of mice given control Th cells. Thus, Th cell responses can clearly contribute to resistance to mycoplasma infection as effector cells as well as promote the development of inflammatory lesions associated with the disease.

T helper subsets—The activation of different Th cell populations and the regulation of these responses are likely critical to the outcome of mycoplasma disease. As described above, Th1 and Th2 cell subsets are two functionally distinct populations of Th cells [91]. Th1 cells are primarily involved in cell-mediated immunity, while humoral immunity is supported by Th2 cell activity. Although the role of Th cell subsets is unknown for mycoplasma diseases, Th1 and Th2 cells can determine the outcome of infections and other diseases [92–94]. Our previous study [89] demonstrated that both Th1- and Th2-type responses were present in the lungs of mycoplasma-infected mice. Because IFN-γ and IL-4 are known mediators in controlling the Th1/Th2 bias in a given immunologic environment [58], we took advantage of the availability of IFN-$\gamma^{-/-}$ mice, which should have a more Th2 polarized response to mycoplasma, and IL-$4^{-/-}$ mice, which should preferentially have a Th1 polarized response. Indeed, we found this is what occurs after infection or

immunization [53]. Using IFN-γ $^{-/-}$ mice or IL-4$^{-/-}$ mice, Woodlard *et al*. performed a series of studies to determine the role of these cytokines in mycoplasma disease. Loss of either IFN-γ or IL-4 has no significant effect on the upper respiratory tract in terms of disease pathogenesis or clearance of the microorganism from the nasal passages. However, the loss of IFN-γ in the lower respiratory tract (lungs) results in more severe disease and increased lesion scores as well as increases in the number of mycoplasma, and these differences were linked predominantly to the role of IFN-γ in innate immunity [95]. In contrast, IL-4$^{-/-}$ mice did not develop more severe disease [53], but there was a trend towards lower numbers of mycoplasma in the lungs of IL-4$^{-/-}$ mice by day 14. In recent studies, we further examined the role of these cytokines in the generation of protective immunity [96]. Prior immunization of the IFN-γ$^{-/-}$ mice led to an increased severity of *M. pulmonis* disease and inefficient clearance of mycoplasma from both the upper and lower respiratory tracts. Immunized IL-4$^{-/-}$ mice on the other hand were far better protected, exhibiting less disease severity and a dramatically enhanced ability to clear the mycoplasma, as compared to wild type mice. These results indicate that IFN-γ is a key cytokine influencing the generation of protective adaptive immunity against mycoplasma infections, whereas IL-4 interferes with the development of optimal immunization and contributes to the generation of inflammatory lesions.

The impact of the regulatory cytokines, IFN-γ and IL-4, is complex. For example, Th2 cell responses in the lung are linked to IL-4 dependent inflammatory reactions that occur during allergic asthma airway hypersensitivity reactions [97]. Infections of *M. pneumoniae* are implicated in the exacerbation of asthma, but the mechanism behind exacerbated airway hypersensitivity reaction (AHR) caused by respiratory infections is unknown [8-98-99]. Woolard *et al*. demonstrated that IL-4 independent pathways were responsible for the exacerbation of methacholine-induced airway hyperreactivity associated with mycoplasma infections. IL-4 deficiency in mice, in contrast to our expectations, increases the severity of airway hyperreactivity due to mycoplasma infection [100]. So, although IL-4 may promote inflammatory lesions and interfere with optimal immunization against mycoplasma, this cytokine dampens the physiologic effects of mycoplasma infection that may contribute to exacerbation of other respiratory diseases, such as asthma. Furthermore, our results using IFN-γ $^{-/-}$ or IL-4$^{-/-}$ mice that show altered responses against mycoplasma may not be due to direct effect of these cytokines. Recent studies from our laboratory [96] demonstrate that a deficiency in a single cytokine, either IFN-γ or IL-4, results in a significant shift in the expression of a number of cytokine and chemokine genes in the lung as compared to the wild-type mice. The changes are apparent in both naïve and infected lungs. Further work is needed to understand the breadth of the effects that IL-4 and IFN-γ have on host responses against mycoplasma infection. However, our results are consistent with the hypothesis that Th1 responses are responsible for resistance to *M. pulmonis* infection, perhaps by IFN-γ mediated activation of macrophage killing [101]. In contrast, Th2 responses appear ineffective in controlling mycoplasma infection and as a result promote inflammatory disease.

T regulatory cells—T_{reg} cells are a heterogeneous T cell population thought to maintain immunologic balance and prevent or minimize tissue damaging immune responses [102–104]. These cells inhibit a wide range of autoimmune and inflammatory reactions, such as gastritis, oophoritis, orchitis, thryoidititis, inflammatory disease (IBD) and spontaneous autoimmune diabetes. T_{reg} cells are also shown to control the persistence of a *Leishmania major* infection [105–106] and severity of inflammation associated with a number of pathogens. $CD4^+CD25^+$ T_{reg} cells can suppress the cytokine production and proliferation of conventional $CD4^+$ $CD25^-$ T cells [107–108]. However, studies of the T_{reg} cell effects on Th cell subsets are conflicting with some studies suggesting dampening of Th2 responses and others indicating promotion of Th2 cell responses [109–110]. Classical T_{reg} cells are

defined as $CD4^+CD25^{hi}FoxP3^+$, and these cells are known to act against the inflammatory response by secreting cytokines such as IL-10 and TGF-β, as well as through Fas-FasL engagement [111–112]. Other possible mechanisms of suppression by T_{reg} cells involve IL-35 secretion, granzyme-mediated cytotoxicity, and cytokine sequestration, though these are still being examined [113–115]. T_{reg} cells have a major role in modulating immune and inflammatory responses that have the potential to cause damage to the host if not tightly controlled.

As T_{reg} cells are involved in the regulation of immune responses and play an important role in a number of other respiratory diseases [116–118], we are currently studying the role of T_{reg} cells in *M. pulmonis* disease. Ongoing studies [119] from our laboratory demonstrate increases in T_{reg} cells in lungs and lower respiratory draining lymph nodes after mycoplasma infection. To assess their role in mycoplasma disease, we are taking advantage of *in vivo* depletion of T_{reg} cells using an antibody against the surface protein CD25. This model has been used a number of times previously with success [120–121], and flow cytometry indicates that T_{reg} cells are selectively depleted without significant changes to other cell populations [122]. Mice were administered anti-CD25 monoclonal antibody and infected with *M. pulmonis*. Depletion of T_{reg} cells results in a dramatic increase in disease severity. In mice are T_{reg} cell depleted, significant weight loss (nearly a 30% reduction in body weight) occurred, whereas mice that are not T_{reg} cell depleted lost slightly more than 5% of their body weight. In addition, depletion of T_{reg} cells leads to a significantly higher incidence of pulmonary lesions than observed in non-T_{reg}-depleted mice. However, as was the case with depletion of $CD8^+$ cells, the depletion of T_{reg} cells does not affect mycoplasma numbers in the lungs. This increase in disease severity in $CD25^+$ depleted mice also corresponded with significantly higher titers of mycoplasma-specific IgG, IgM, and IgA in the serum as compared to non-Treg-depleted mice. Thus, these data are consistent with the idea that depletion of T_{reg} cells prior to mycoplasma infection leads to stronger immune responses, contributing to more severe disease. Furthermore, the numbers of mycoplasma in lungs did not change, demonstrating that the increased inflammatory responses in the absence of T_{reg} cells do not result in clearance of the organism and that T_{reg} activity does not promote persistence of infection, as indicated in other respiratory diseases [119].

T helper 17 (Th17) cells—Th17 cells are one of the newest subsets of T cells to be identified and are characterized as activated CD4+ T cells secreting interleukin-17 (IL-17). As stated earlier, IL-17 can be crucial to the clearance of viral, bacterial and fungal pathogens [73–75]. The production of IL-17 induces the mobilization of neutrophils to the inflammatory site through a production of various chemokines and cytokines, and it is this role that makes Th17 cells important for defense against these pathogens [123]. Th17 cells may also be involved in chronic inflammatory conditions; for example, mice, incapable of making IL-17, have decreased susceptibility to the development of autoimmune diseases [59-123-124]. Thus, Th17 cells play a unique role in host defenses through their ability to promote recruitment of neutrophils to sites of infection or disease.

The first indication of the presence of IL-17 in mycoplasma respiratory disease was the observation that IL-17 mRNA transcripts increased in the lungs of *M. pulmonis* infected mice [125]. Later studies revealed the detection of IL-17 protein in the bronchoalveolar lavage fluid of *M. pneumoniae* infected mice and pulmonary $CD4^+$ T cells from infected mice were shown to be the source of IL-17 [126]. Further analysis revealed that increases in IL-17 corresponded with the recruitment of neutrophils in response to *M. pneumoniae* infection. In additional studies, we demonstrated that Th17 cells indeed have a role in mycoplasma disease [127]. Resistant C57BL/6 mice were infected with *M. pulmonis*, and IL-17 production by lymphocytes from the lungs and cervical lymph nodes was found. $CD4^+$ T cells were identified as the source of IL-17. To determine the protective effects of

these Th17 cells, IL-17 receptor (IL-17R) $^{-/-}$ knock out mice were infected with *M. pulmoni*s and compared to the wild-type mice. The IL-17R$^{-/-}$ mice have a significantly increased bacterial burden both in the nasal passages and in the lungs when compared to wild type mice demonstrating that IL-17R$^{-/-}$ mice are more susceptible to mycoplasma respiratory infections. Additionally, infected mice depleted of neutrophils had a significant increase in mycoplasma numbers recovered from both the nasal passages and the lungs. Interestingly, we also found that activation of Th17 cells during mycoplasma infection conferred resistance to an unrelated pathogen, *Listeria monocytogenes* [127]. Thus, the secretion of IL-17 by Th17 cells and the corresponding recruitment of neutrophils play an important role in the protection of the host from mycoplasma respiratory disease. Further studies are needed to determine whether Th17 cells are involved in controlling mycoplasma numbers in other, more susceptible, strains of mice. In addition, the role of Th17 cells in the pathogenesis of chronic inflammation should be examined.

CD8$^+$ T cells—In comparison to Th cells, CD8$^+$ T cell responses are a smaller component of the total T cell response against mycoplasma infections. In our studies on T cell responses in *M. pulmonis* respiratory disease [89], the appearance of mycoplasma-specific CD8$^+$ T cells was unexpected. We expected a Th cell response as exogenous antigen is preferentially processed and presented in the context of Major Histocompatibility Complex II (MHC II), which is the common pathway for most extracellular pathogens. However, the major pathway for CD8$^+$ T cell activation is through the presentation of antigenic peptides derived from intracellular pathogens bound to MHC I. In support, nasal-pulmonary immunization results in the generation of Th, but not CD8$^+$ T cell, responses in the lungs [128]. Some mycoplasma can have intracellular phases [129–130], but *M. pulmonis* has not been found to do this [131]. Most likely, cross presentation of antigen by dendritic cells is responsible for CD8$^+$ T cell activation. Cross-presentation refers to the ability of dendritic cells to present exogenous antigen in the context of MHC I [132]. In fact, ongoing studies in our laboratory [133] demonstrate that exogenous mycoplasma antigen given to pulmonary dendritic cells *in vitro*, which in turn activate both mycoplasma-specific Th and CD8$^+$ T cells. Further studies are needed to demonstrate that cross-presentation by dendritic cells is responsible for CD8$^+$ T cell activation in mycoplasma infections. However, it is clear that CD8$^+$ T cell responses, in addition to Th cell responses, are induced in the lungs after mycoplasma infection.

A regulatory role for CD8$^+$ T cells mycoplasma respiratory disease was first suggested in studies of resistant and susceptible strains of rats [14-15-134]. We found that F344 rats, which develop less severe disease after *M. pulmonis* infection, had a relatively larger proportion of CD8$^+$ T cells to Th cells in their lymphoid tissues and lungs as compared to the susceptible LEW rat strain [134]. We suggested that CD8$^+$ T cells may suppress the Th cell responses against mycoplasma, resulting in less severe disease [134–135]. As described above, *in vivo* depletion of CD8$^+$ T cells in *M. pulmonis* infected mice resulted in a dramatic increase in disease severity, confirming that CD8$^+$ T cells do dampen mycoplasma associated inflammatory responses [89]. The mechanisms through which CD8$^+$ T cells dampen inflammatory lesion development are not clear. Consistent with our ongoing hypothesis that Th2 cell responses are responsible for the immunopathology, IFN-γ secretion by CD8$^+$ T cells may skew the responses toward Th1-type responses and dampen Th2-type responses. Alternatively, mycoplasma-specific CD8$^+$ T cells could kill antigen-presenting cells, thereby reducing the ability of Th cells to be activated. Thus, CD8$^+$ T cells play a significant role in modulating the inflammatory reactions during the pathogenesis of mycoplasma pulmonary disease, but further studies are needed to elucidate the mechanisms through which these cells can have such a dramatic impact on disease severity.

Mechanisms Influencing T Cell Responses: By understanding the mechanisms involved in regulating different T cell reactions, novel approaches to prevent or treat mycoplasma and

other inflammatory diseases of the respiratory tract can be developed. However, the regulation of T cell responses is extremely complex. In the previous section, we described how Th cells could have both beneficial and detrimental effects on events that occur after mycoplasma infection. Data are consistent with the hypothesis that Th1 responses contribute to resistance from infection, while Th2 responses promote the inflammatory responses. In addition, both $CD8^+$ T cells and T_{reg} cells dampen the inflammatory responses associated with mycoplasma disease. The remainder of this article will focus on two current areas of interest, dendritic cells and natural killer (NK) cells and their role in modulating mycoplasma immune responses. Dendritic cells are extremely potent antigen presenting cells that help activate T cell populations. NK cells are a lymphocyte population that like $CD8^+$ T cells, kill target cells and produce cytokines; however, unlike $CD8^+$ T cells, they are not antigen specific. We have recently found that both of these cell populations can influence the progression of *M. pulmonis* disease or modulate immune responses against this pathogen. There are a number of other factors that could also influence T cell response, including the production of chemokines (chemotactic cytokines), hormones, the nature of the antigen, other infections, etc., but these are beyond the scope of the current review.

Regulation of T cell Responses by Dendritic Cells—Dendritic cells (DCs) are extremely potent antigen-presenting cells, which can activate both Th and cytotoxic T cells and are found in lungs [136–142] as well as other tissues. In skin, lungs, liver or other tissues, DCs are typically in an immature state, characterized by low expression of costimulatory molecules and increased ability to sample the environment though endocytosis to search for antigens [143–144]. When an antigen is endocytosed, it is processed and presented in the context of Major Histocompatibility Complex II (MHC II), or in the case of cross-presentation, MHC I. The DC presents the digested antigen to a corresponding T cell via the T cell receptor complex (TCR). In order to active naïve T cells, the DC is stimulated to maturity through recognition of pathogen components, such as endotoxin and lipoproteins of bacteria, or by cytokines released from host cells. The maturation of DCs often occurs during the translocation from the site of infection to the nearest lymph node [143–144]. One of the key features of mature DCs is that they express higher levels of co-stimulatory molecules and therefore more capable of providing the final activation signal to T cells. In addition, DCs produce cytokines that help activate and shape the ensuing T cell response.

Respiratory DCs are found throughout the respiratory tract and within and below the airway epithelium, in the nasal mucosa, lung pleura, connective tissues and in the alveolar air spaces [144–145]. During steady state conditions, DCs within the airways provide immunologic surveillance of all particulate matter inhaled. In the absence of disease or infection, these airway DCs are present in an immature state. In support, we have shown that resident $CD11c^+$ dendritic cells in murine lungs do not express high levels of co-stimulatory molecules and are not fully matured [133]. This indicates that the lung is typically not a site where immune responses are initiated. Furthermore, a large majority of the particulate matter that is inhaled is harmless, and adaptive immune responses are not needed and could actually be detrimental. In these cases, the inert particles do not elicit a strong maturation responses, and the immature airway DCs carry these harmless particles or antigens to the nearest draining lymph nodes. Because of the lack of co-stimulatory molecules on the DCs, the induction of tolerance occurs rather than specific T cell activation[144–145]. In the case of a pathogen, such as mycoplasma, airway DCs are stimulated to mature through signals mediated by toll-like receptors (TLR), cytokine receptors, etc. The mature DCs would then be capable of activating antigen specific T cells. Thus, DCs along the respiratory tract are critical in the host's ability to differentiate between antigens that are innocuous and those for which immune responses should be generated.

While respiratory tract DCs are very important in promoting adaptive immunity responsible for resistance against pathogens and recovery from infections, pulmonary dendritic cells involved in respiratory diseases are capable of driving T cell responses within the lung that contribute to the pathogenesis of these inflammatory reactions. Numbers of dendritic cells in lungs can increase in inflammatory disease [146–148]. In support of a role of dendritic cells in the induction of immune-mediated inflammatory disease, studies suggest that dendritic cells are critical in the generation of allergic and asthmatic responses [149–152]. Both asthma and allergic reactions are overreactions to harmless allergens in the air. An asthma attack presents as constriction of the airways due to inflammation caused by an influx of immune cells, particularly eosinophils, ultimately limiting the amount of oxygen exchange [144], and these reactions are associated with increases in the number of airway and myeloid DCs [146-153-154]. In support of DCs role in mediating these reactions, mice intratracheally given bone marrow derived myeloid $CD11c^+$ DCs pulsed with antigen generate increased Th2 response and eosinophilic airway inflammation after re-exposure to the antigen [150-151-155]. In addition, ablation of DCs [156–157] prior to challenge with a model allergen results in virtual elimination of airway hyperreactivity responses and a reduction the production of Th2 cytokines [149–158]. Adding pulsed DCs back to these ablation models restores the airway hypersensitivity reactions of the asthma. These are some of the clearest studies that demonstrate $CD11c^+$ dendritic cells in the lungs can mediate inflammatory and other adverse reactions along the respiratory tract and support the idea that DCs are likely critical in generating immune responses in chronic mycoplasma respiratory diseases.

Most likely, dendritic cells contribute to the immune-mediated pathology of mycoplasma respiratory disease. However, the role of dendritic cells (DC), macrophages and other antigen presenting cells in modulating immunity in mycoplasma disease is unknown. We have begun exploring the possible role of DC in the lungs of *M. pulmonis* infected mice. There is a significant increase in the number of $CD11c^+$ DCs in the lungs of mice at 14 days after mycoplasma infection [133]. The DCs appear to be more mature or activated as the expression of co-stimulatory molecules CD80 and CD86, and MHC II is increased in DCs isolated from lungs of infected mice. In addition, macrophages and DCs show different patterns of cytokine mRNA expression, which supports the idea these cells have different impacts on immunity in response to infection. In fact, DC containing cell populations from the lungs of infected mice are most capable of stimulating mycoplasma-specific Th and $CD8^+$ T cell responses *in vitro*. In contrast, DC from naïve animals and macrophages from either naïve or infected animals were significantly less effective in supporting T cell responses. Most interestingly, we also found that DCs, not macrophages, are localized in the inflammatory lesions in the lungs of infected mice, and these DCs were directly interacting with Th cells present in the inflammatory infiltrates. Thus, DC cells appear to be the major antigen presenting cell population responsible for pulmonary T cell stimulation in mycoplasma-infected mice and likely contribute to Th cell mediated inflammatory responses involved in disease pathogenesis.

Dendritic cells may also be a major factor in determining the type of immune reactions stimulated in mycoplasma respiratory disease. DCs can also modulate the types of immune responses generated. For example, DCs from Peyer's patches preferentially stimulate Th2 responses while splenic dendritic cells promote Th1 type responses [159–160]. Similarly, studies [137] demonstrate that resident dendritic cells from rat lungs preferentially stimulate Th2 responses. We [52] and others [161–162] have shown that resident Th cells in murine lungs are primarily Th2 like. Further studies indicate that different populations of DCs can be defined by their expression of cell surface markers, such as CD8α, CD11b, and DEC 205. These distinct DC populations promote differentiation of distinct Th cell responses [163–167]. However, studies do suggest that cell surface markers alone cannot be used to predict

DC activity or function [168–171]. Different factors can influence the ability of dendritic cells to support Th cell subsets or cytotoxic T cell responses [168–172]. For example, IL-4, histamine or norepinephrine polarizes dendritic cells into Th2 cell-promoting dendritic cells while IL-12, IFN-γ or LPS treated dendritic cells preferentially support Th1-type responses. Ongoing studies in our laboratory demonstrate that bone marrow derived DCs, differentiated in the presence of IL-10 and TGF-β, can influence the outcome of mycoplasma infection [173]. We pulsed these DCs with mycoplasma antigen and intratracheally inoculated them into naïve mice. When infected with *M. pulmonis*, these mice developed more severe respiratory disease, as compared to mice inoculated with DCs derived using GM-CSF and IL-4. Thus, it is clear that dendritic cells not only have a central role in the initiation of immunity to mycoplasma disease, but they also have the potential to influence the type of T cell responses generated, thereby determining the outcome of disease.

Future studies are needed to understand the impact of dendritic cells, as well as other antigen presenting cells, have on the development of protective immunity against mycoplasma as well as their participation in disease pathogenesis. Importantly, we propose that manipulating dendritic cells and other antigen presenting cells can predictably promote the harmful or beneficial effects of T cell responses in mycoplasma disease.

NK cells can affect mycoplasma-specific T cell responses—NK cells are lymphocytes of the innate immune system that are involved in the early defense against foreign cells and autologous cells undergoing various forms of stress, such as microbial infection or tumor transformation [174]. NK cells also produce cytokines, such as IFN-γ, tumor necrosis factor-α (TNF-α) and granulocyte macrophage-colony stimulating factor (GM-CSF), and chemokines such as CC chemokine ligand 3 (CCL3; macrophage inflammatory protein 1-α (MIP1-α), CCL4 (MIP1-β) and CCL5 (RANTES), when stimulated with susceptible target cells. Early studies indicated that NK cells are an important early source of IFN-γ early in the innate immune response to mycoplasma disease and important for clearance of the organism in C57Bl/6 mice [175]. More recent studies confirmed that NK cells are the major population in the lungs producing IFN-γ as early as three days after mycoplasma infection of BALB/c mice [95]. To determine if NK cells had a direct effect on mycoplasmas, perforin granules were isolated from NK cells and cocultured in a serial dilution of mycoplasma; the mycoplasma, at any dilution, were untouched. Surprisingly, depletion of NK cells from IFN-$\gamma^{-/-}$ mice prior to infection leads to a more effective clearance of mycoplasma from the lung than NK cell competent IFN-$\gamma^{-/-}$ mice; this effect was not seen in NK depleted wild type mice. There were also lower levels of inflammatory cytokines and less infiltration of neutrophils in the lungs of the NK depleted IFN-$\gamma^{-/-}$ mice, indicating a corresponding decrease in inflammatory disease. These results demonstrate that in the absence of IFN-γ, NK cells can dampen innate immune mechanisms that help control mycoplasma numbers in the lung.

Although NK cells are the primary effector cells of the innate immune system [176], they also are able to influence the adaptive immune responses [177–182]. NK cells can regulate adaptive immune responses through the production of Th1-type cytokines early after viral infection [183] or through the activation of dendritic cells [184]. The depletion of NK cells before immunization with a model allergen inhibits pulmonary eosinophilic and T cell infiltration with decreased levels of IL-4, IL-5 and IL-12 in the bronchoalveolar lavage (BAL) fluid in a murine model of allergic asthma [185]. Similar to what we found in innate immunity [95], we hypothesized that NK cells would modulate, and perhaps play a detrimental role, in the generation of mycoplasma-specific adaptive immune responses that resist infection. In a recent study [90], we sought to determine the impact of NK cells on the development of protective adaptive immunity in response to nasal-pulmonary immunization against mycoplasma. Depletion of NK cells prior to nasal-pulmonary immunization

enhanced resistance to mycoplasma respiratory infection. The effect of NK cells on the generation of protective immunity in lungs was dependent on lymphoid cells, as immunization of either SCID mice or immunocompetent mice depleted of $CD4^+$ T cells did not demonstrate any increased resistance in the presence or absence of NK cells. The presence of NK cells at the time of nasal-pulmonary immunization modulated mycoplasma-specific cytokine responses in lungs and lower respiratory nodes. In particular, NK cells skewed the mycoplasma-specific T cell cytokine responses in the draining lymph nodes to produce higher IL-4, IL-13 and IL-17 levels while lowering IFN-γ responses. Adoptive transfer of total lung lymphocytes isolated from immunized mice into naïve mice led to a significant reduction in the mycoplasma numbers in lungs, and the resistance was greater if cells were obtained from immunized mice which were depleted of NK cells. The primary effect of NK cells is on Th cells, and surprisingly, the data suggests that NK cells skew the T cell responses toward the Th2-type, which as described above, is not effective in resistance to mycoplasma infection. Thus, NK cells are one of the factors that influence the Th1/Th2 balance, and that optimal approaches for vaccination may require minimizing the impact of NK cells on Th cell responses during the generation of protective adaptive immunity.

Perspectives And Conclusions

Mycoplasmas are ubiquitous pathogens with the ability to infect a wide variety of hosts causing significant biomedical and economically important diseases. In general, these agents cause persistent infections with subclinical and clinical disease. Because of the chronic nature of these infections, it is likely that almost every component of the host immune system is involved. The ability of mycoplasma infections to persist despite the intense immune and inflammatory responses demonstrates that these organisms have very complex interactions with the host. While the immune responses of some hosts can resist mycoplasma infections, they can also contribute to disease pathology in other hosts resulting an apparently frustrated and ineffective response against the mycoplasma infections. T lymphocytes are a major component of the immune response against mycoplasma infection. Because T cells modulate most immune responses, the progression of mycoplasma respiratory disease is dependent on the balance between those T cell responses that may promote protection, and those that evoke immune-mediated pathogenesis. In this review, we summarized studies that demonstrate the contrasting roles of T cells in host resistance and pathogenesis and discussed the influence that other immune cells have on the outcome of these responses.

Understanding the interplay between the immune cell types has proved challenging, particularly in defining the specific roles of a single immune cell during mycoplasma disease progression *in vivo*. However, we have been able to determine some important influences of different T cell subsets as well as innate immune cell subpopulations. Both T regulatory cells and Th17 cells, subsets of the T helper cells, demonstrate protective immunity against mycoplasma disease. However, mounting evidence indicates that Th1 polarized environments are more protective than Th2 polarized environments and the cytokines that promote these conditions are also influential in generation of a mycoplasma-specific T cell response. However, we have yet to demonstrate conclusively that the $CD4^+$ T cells from these environments are solely responsible for the pathologic or protective effects, but current studies are designed to address this question. The host's innate immune response and initial cytokines produced by these early responder cells is also very influential over the kind of T cell responses generated against mycoplasma infections, as observed by natural killer cells generating conditions more favorable to the development of Th2 cells in the lower respiratory node. Dendritic cells impact the immune response by activating not only CD4+ T cells found at the pulmonary lesion sites in mycoplasma infected mice, but also presenting antigen through cross presentation to CD8+ T cells, which dampen the inflammatory

response. However, efforts to skew the *in vivo* T cell response using bone marrow derived dendritic cells surprisingly results in quicker disease progression and increased pulmonary pathology. With our ongoing studies we will continue to dissect each of these individual components to better understand what leads to protective immunity.

While there is currently no effective vaccine against mycoplasma, investigations have begun to reveal key components of host immune response/mycoplasma interactions that participate in surveillance and disease pathogenesis. Utilizing approaches such as genetically engineered knock out animal models deficient in T cell cytokine production or adoptive transfer of lymphocytes, studies will continue to shed more light on the mechanisms that impact resistance to and progression of mycoplasma disease. Hopefully, such studies will elucidate methods to preferentially activate T cell mediated immune responses that confer protection while minimizing immune-mediated lung damage leading to the development of novel vaccines against mycoplasma diseases.

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