Chapter 4

REGULATION OF LUNG IMMUNITY: SIGNIFICANCE OF THE CYTOKINE ENVIRONMENT

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INTRODUCTION

The disruption of lung structure and pulmonary function can be a devastating event leading to acute deteriorating health and chronic respiratory illness (1-4). Regulation of lung function is maintained by intricate mechanisms that promote a balance between host defenses against injurious events and reactive inflammatory responses. An excessive inflammatory response can result in acute lung injury (ALI), leading to organ dysfunction. The development and regulation of inflammation and immune responses within the lung are dependent upon several complex interactions including the nature of the infectious agent, structural cell production of chemotactic factors, activation of recruited leukocytes, and release of specific cytokines. The cytokine responses that occur in the lung dictate the nature of ensuing activation events and the type of immune response that subsequently occurs. For example, if an infectious or noxious foreign agent initiates a response that predominantly induces a Th1 type response characterized by high levels of IL-12 and IFN-γ, an environment may be initiated that would augment subsequent anti-pathogen immune responses within the lung. In contrast, if a foreign agent induces a predominant Th2 type response, then subsequent responses may be skewed. The Th2 response may alter the ability to clear intracellular pathogens and increase the host's susceptibility to developing allergic responses. This chapter will address the influence of early cytokine production on the nature of the subsequent immune responses.

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Regulation of ALI and Cytokine Responses in Sepsis

The induction of septic shock is commonly associated with bacterial infections and an intense systemic inflammatory response that leads to severe physiologic and immunologic dysfunction of multiple organs (5-10). The lung is one of the most common target organs in septic patients, often necessitating the use of mechanical ventilatory support. Within the lungs of septic patients, local production of inflammatory cytokines and chemokines initiate an intense and sustained inflammatory response resulting in the lung injury associated with the acute respiratory distress syndrome (ARDS), tissue remodeling, and eventual respiratory failure. A number of inflammatory cytokines and chemokines have been identified in patients that develop ARDS, including TNFα, IL-1β, MIP-1α, and IL-8. Recent evidence in animal models, however, suggest that the deleterious effects induced by the inflammatory cytokines can be counterbalanced by endogenous anti-inflammatory cytokines and chemokines produced locally within the lung (11-15). These anti-inflammatory cytokines can be broadly characterized as type 2 cytokines.

A number of investigators have established that a significant increase of interleukin-10 (IL-10) production, both systemically in the circulation and locally within the lung, is associated with sepsis and ARDS (13, 16, 17). It remains controversial, however, as to whether these responses correlate to the development of or the protection from septic responses. There is no doubt that IL-10 is a potent anti-inflammatory cytokine that can down-regulate TNFα and other inflammatory stimuli, as well as most chemokines (see Chapter 17). However, recent studies in animal models of sepsis employing cecal ligation and puncture (CLP) have demonstrated that IL-10 produced locally within the lung can lead to increased susceptibility to severe bacterial infections (14, 18). The occurrence of secondary infections during sepsis is often an initiator of or contributor to the progression of ARDS. Thus, although IL-10 may have a beneficial systemic effect by regulating over-production of proinflammatory cytokines, IL-10 locally in the lung may decrease the immune response mounted against secondary infections.

A second regulatory type 2 cytokine that has recently gained notice is interluekin-13 (IL-13). This cytokine shares similar features of IL-10 as reflected by its ability to regulate inflammatory cytokine production from mononuclear phagocytic cells. Although no IL-13 has been detected in the plasma of patients with sepsis or in volunteers receiving endotoxin (19), studies in animal models have demonstrated that IL-13 may have protective effects in septic-like responses (19-22). In a recent report using a CLP model of sepsis, IL-13 was found only in the tissues of the septic animals with no detectable levels in the serum (23). Thus, IL-13 appears to play a local role at the organ level. The administration of exogenous recombinant IL-13 to animals undergoing lethal septic responses protected them from death. In these same studies, the neutralization of IL-13 caused a significant increase

in lethality associated with increased levels of inflammatory and chemotactic cytokines.

Unlike IL-10, IL-13 has the ability to differentially induce a number of chemokines from various cell populations (24-28). For example, although IL-13 can downregulate the production of neutrophil chemotactic CXC and CC chemokines, such as IL-8 and MIP-1α, it is known to induce the production of other CC chemokines, such as MDC, C10, and MCP-1. The preferential induction of certain chemokines by IL-13 suggests that these chemokines may play a specific role in protection against the septic response. A number of studies have demonstrated that IL-13-inducible chemokines play a key role in the regulation of bacterial clearance and protection from the adverse effects of septic responses (23, 30, 31). Thus, IL-13 not only modulates inflammatory cytokines that may lead to unchecked pulmonary inflammation, but also augments bacterial clearance guarding the host from opportunistic infections.

The novel observations that specific chemokines have the ability to augment anti-bacterial immune responses suggested that these molecules might have therapeutic potential. The administration of exogenous MCP-1 to mice undergoing LPS-induced septic responses attenuated the lethal response (32). In addition, the administration of anti-MCP-1 antibody increased mortality in mice subjected to a sublethal dose of endotoxin. In both cases, the effects appeared to be correlated to the levels of TNFα and IL-12, suggesting that MCP-1 may modulate inflammatory cytokine production. Other studies have also demonstrated that MCP-1 can increase bacterial clearance via the upregulation of macrophage bactericidal activity (33). Studies further examining the role of the IL-13-inducible chemokines (C10 and MDC) have shown that these chemokines have a significant effect on the septic response (31, 34, 35). In a model of CLP-induced bacterial peritonitis, the effect of these two CC chemokines was primarily on bacterial clearance with little effect on inflammatory cytokines, such as IL-12 and TNFα. The ability of these IL-13-induced chemokines to facilitate more efficient clearance of bacteria also modulated production of both the systemic inflammatory cytokines and lung neutrophil chemokines. Thus, controlling the response more efficiently at the site of bacterial contamination led to a lower incidence of both systemic inflammation and remote organ dysfunction. These studies demonstrate how cytokines, such as IL-13 and IL-13-inducible chemokines, with a traditional role in antigen-specific immune responses, can impact on the innate immune response and control the deleterious outcome of a disease.

Chemokines: A Family of Cytokines with Diverse Functions

Historically, chemokines have been viewed as leukocyte chemoattractants that regulate cellular movement from the circulatory system

into inflamed tissue. However, as investigators continue to examine the function of chemokines in both disease and homeostatic circumstances, one finds a complex regulation of function and interaction among multiple cell types. Chemokine receptors identified on various structural cells, mediate functions ranging from chemotaxis to growth regulation to activation. As reviewed in the chapter by Strieter and colleagues (see Chapter 3), chemokines have been primarily divided into two main families based upon their sequence homology and the position of the first two cysteine residues (36, 37). This group of chemoattractants has grown considerably over the years as groups have utilized microarray technology with expressed sequence tab databases (38). As this continues, however, the function of all of these members must be characterized in order to determine their individual role in the inflamed and non-inflamed environment. Two other distinct families are the C family and the CXXXC family. Both of these families have only a single member, lymphotactin and neurotactin (fractalkine), respectively.

Although a number of chemokines have been identified as lymphocyte activating factors, the exact role that each chemokine plays during an immune response remains incompletely defined. When examining T lymphocytes skewed toward a type 1, or type 2, response *in vitro* it appears that there is preferential expression of certain chemokine receptors. T lymphocytes that have a type 1 phenotype (characterized by IFN-γ production) appear to preferentially express CXCR3 and CCR5. T-cells that are skewed toward a type 2 phenotype preferentially express CCR3, CCR4, CCR8, and CXCR4 (39-46). It is interesting to speculate as to whether these receptors are the cause, or result of, lymphocyte differentiation. It is conceivable, however, that these receptors would dictate the ligands required to allow these cells to migrate into inflamed tissues. Indeed, if chemokine production is examined during specific types of immune responses, distinct chemokine phenotypes can be observed. During type 1 immune responses, there appears to be a predominant dependence on MIP-1, RANTES, and interferon-inducible protein-10 (IP-10). In contrast, during type 2 immune responses one can observe the preferential expression of eotaxin, MDC, TARC, and TCA3 (40, 43, 47-53). A number of the studies that described these observations established the importance of these molecules during the immune response by neutralization experiments. These latter chemokines are induced by the type 2 cytokines, IL-4 and IL-13, thus correlating the type 2 immune response to the chemokines and the chemokine receptors that are expressed on Th2 lymphocytes. Thus, the local production of certain chemokines could dictate the type of lymphocyte recruited to the lung. Because these correlations in animal models are not exclusive, one must be cautious about extrapolating the significance of these findings to human disease states. It remains intriguing to speculate on how to therapeutically target specific chemokines or chemokine receptors during unique diseases that demonstrate a predicted cytokine phenotype.

The functions of chemokines have been expanding over the past several years and it is now evident that they modify the immune response either directly by activating the antigen presenting cell (APC) and T lymphocyte, or indirectly by recruiting the proper cell populations. Initial studies found that CC family chemokines (RANTES, MIP-1α and MIP-1β) could effectively initiate an antigen specific response *in vivo* when used in place of an adjuvant such as Freund's complete adjuvant (54). These early studies led to the hypothesis that chemokines could effectively skew immune responses toward either a type 1 (IFN–γ producing) or a type 2 (IL-4 producing) response (53, 55-59). It now appears that chemokines not only have the ability to recruit specific subsets of lymphocytes, but also can aid in determining the type of immune response that occurs (Table 1). These and other aspects may have a significant effect on the development of immunity within the lung.

Table 1. The role of specific chemokines in skewing the immune response

Chemokine	Receptors	Functions
RANTES	CCR1, CCR5	Recruits monocytes and lymphocytes; Skews towards type Th1 immune response
MIP-1α	CCR1, CCR5	Directs a Th1 immune response; Upregulates dendritic cell-derived IL-12 production
MCP-1	CCR2	Recruits monocytes, lymphocytes and basophils; Directs a Th2 immune response; Decreased IL-12 and increases IL-10
TCA3	CCR8	Recruits neutrophils and Th2 lymphocytes; Directs a Th2 immune response
IP-10, MIG, ITAC	CXCR3	Recruits monocytes and lymphocytes; Skews the immune response to Th1 type
SDF-1α	CXCR4	Recruits naïve and Th2 lymphocytes; May skew the immune response to Th2 type

The Role of Chemokines in Anti-bacterial and Anti-mycobacterial Immune Responses

The induction of immune responses during bacterial infections in the lung relies on an effective activation of innate immune responses that can clear the organisms before they colonize the lung. Examinations of bronchoalveolar lavage (BAL) samples from patients with pneumococcal and pseudomonal pneumonias have shown high levels of IL-8 (8, 60-64). These early studies posed the hypothesis as to whether the presence of this potent neutrophil chemoattractant was beneficial or detrimental to the clearance of the microorganism and health of the lung. A number of *in vivo* studies have addressed the importance of chemokines in initiating and maintaining an effective anti-bacterial response. In a model of *Klebsiella pneumoniae* infection in the lungs of mice, the influx of neutrophils mediated by MIP-2 (functional homologue of IL-8), were found to be required for the

early clearance of the bacteria. Interestingly, the neutralization of MIP-2 had little effect on the eventual survival of the mice (65). Similar findings were observed in a rabbit model of *E. coli* infection that examined the role of another IL-8 homologue, GRO-α (66). These data suggested that perhaps multiple CXC chemokines expressed during bacterial pneumonia could compensate for the neutrophil recruitment and anti-bacterial effect even in the absence another CXC chemokine (67). In support of this concept, when KC (another CXCR2 ligand with IL-8 homology) was overexpressed during *Klebsiella* infection in mice, a significant effect on bacterial clearance and enhanced survival was observed (68). In other studies in which the primary murine neutrophil chemokine receptor CXCR2 was blocked, it was observed that this pathway was the most critical for neutrophil recruitment and bacterial clearance (67, 69). Interestingly, because of the redundancy of the CXCR2 ligand system, blocking only one of the chemokines was not as effective as blocking the receptor itself. These studies demonstrated how chemokines, produced locally by macrophage and epithelial cell populations in response to the bacterial infection, could initiate the protective innate immune responses.

These same chemokines have also been identified as being important in other models of pulmonary infections, including *Pseudomonas*, *Nocardia*, and *Aspergillus*. Understanding the regulation of these critical chemokines during pulmonary infections is also important for possibly altering or enhancing bacterial clearance to facilitate disease resolution. For example, neutralization of IL-10 allowed increased CXC chemokine production, associated with increased neutrophil accumulation, and enhanced bacterial clearance and survival (70, 71), indicating an important regulatory mechanism that may be targeted. Altogether, these data demonstrate the central role for these chemokine interactions in anti-bacterial defenses of the lung.

The inability of the pulmonary innate and acquired immune systems to properly dispose of mycobacterial infections has historically had a devastating effect on large populations. More recently the occurrence of new mycobacterial species that are resistant to current therapeutic strategies has led to the re-emergence of this important disease. The ability of this organism to evade the local pulmonary immune response has been targeted by the research community with several important findings resulting from the use of specific animal models. The successful clearance of any intracellular pathogen has been associated with a strong Th1 type immune response, characterized by high levels of IL-12 and IFN-γ. This allows the proper activation of macrophages leading to the intracellular killing of the infecting organism (72-74). The early production of IL-12 by infected macrophages appears to be a key trigger in this response leading to the direct activation of IFN-γ production from infiltrating NK cells and antigen-specific T lymphocytes. However, during infection of macrophages, induction of IL-12 may be directly and/or indirectly regulated by the response to the mycobacterial organism. Although *in vitro* data suggest that

macrophage/dendritic cells infected with mycobacteria produce IL-12 (75, 76, 112), clinical and experimental data suggest that there is a shift in the immune response away from type 1 towards a type 2 response (12-14, 72, 77-79). This shift allows the organism to become established within the lung and impairs the clearance of the mycobacteria.

A critical aspect of bacterial clearance is the recruitment of the correct cell populations, which is in turn dependent upon the upregulation of specific chemokines. As indicated earlier, there appear to be chemokines that are differentially associated with type 1 and type 2 immune responses. Using animal models of mycobacterial antigen-induced pulmonary inflammation, the specific role of chemokines during type 1 immune responses was examined. Examination of granuloma formation in the lungs of mycobacterium-sensitized animals has identified specific chemokines that mediate the formation of the type 1 granulomatous response. In particular, RANTES appears to be a critical cytokine to recruit primarily mononuclear cell populations (56, 79). More interesting, administration of exogenous RANTES increases type 1 immune responses and can down-regulate type 2 immune responses, suggesting that this chemokine may play a regulatory role in recruitment of specific immune cells. Interestingly, it was recently demonstrated that *T. gondii* induces CCR5-dependent, IFN-γ production that is independent of IL-12 (80). Thus, RANTES appears to be associated with the immune response to intracellular mycobacteria.

The primary sources of RANTES in the lung are epithelial cells and macrophages. Thus, the production of RANTES during the initial phases of mycobacteria infection may help to skew the immune response toward a proper Th1 type response to enhance bacterial clearance. Interestingly, mycobacteria infection of epithelial cell populations downregulates RANTES production and may be one mechanism to explain how this organism evades the anti-bacterial immune response (81). In contrast to RANTES production, mycobacteria infection can directly induce MCP-1 production in epithelial cells (82-84), and likewise, MCP-1 is upregulated in severely infected patients with tuberculosis (85). In this context, one might predict that MCP-1 could be involved in a strategy to alter the proper anti-bacterial immune response. A number of studies have now demonstrated that there is an inverse relationship between IL-12 and MCP-1 during an immune specific response (32, 57, 86, 87). Neutralization of MCP-1 during Th2 type granulomatous responses not only decreased the development of the type 2 response but also increased the ability of isolated granuloma macrophages to produce IL-12. In addition, the overexpression of MCP-1 during the development of a type 1 mycobacteria antigen response downregulates the Th1 type cytokines and reduces the IFN-γ-driven pulmonary granulomatous responses.

Additional data using MCP-1 overexpressing and null mutant animals provided further evidence that MCP-1 may alter anti-bacterial immune responses. The overexpression of MCP-1 in transgenic mice

decreased the ability of these animals to clear intercellular pathogens (88). In contrast, in MCP-1 -/- mice type 2 granulomatous responses were downregulated as reflected by decreases in IL-4 and IL-5 expression, while type 1 anti-mycobacteria responses remained intact (89). A final piece of evidence suggesting that MCP-1 can skew the immune response is derived from *in vitro* analysis of T cell activation. In these studies, co-culture of antigen-specific lymphocytes with MCP-1 and antigen caused a significant increase in Th2 type (IL-4) and a decrease in Th1 type (IFN-γ) cytokines (59, 90). Thus, although MCP-1 is an activator of macrophage anti-bacterial responses, it appears that MCP-1 is also involved in skewing the immune response toward a Th2 type response by regulating critical T cell-derived factors. Altogether, these studies suggest that chemokines produced during the initial or innate immune response may impact on the development of pathogen-specific acquired immunity. Furthermore, pathogens such as mycobacteria may directly influence the production of specific chemokines during an anti-pathogen response as a means toward establishing a successful infection.

Host Responses To Viral Infections Can Modulate the Pulmonary Immune Environment

How the host responds to respiratory viral infections can dictate subsequent responses within the lung environment. If the individual responds to a viral infection with a battery of Th1 type cytokines, including IL-12 and IFN-γ, a cellular immune response is promoted and the virus is quickly eradicated (91-95). In contrast, if a Th2 type response is triggered, with IL-4 and IL-13 production, the anti-viral defense may be insufficient and the appropriate cellular immune responses may be attenuated. Recent evidence suggests that respiratory viral infections are a common cause of asthma exacerbations and the response to viral infections may dictate the severity of subsequent asthmatic responses. In particular, respiratory syncytial virus (RSV) is known to cause asthma exacerbations. In many children less than 2 years of age, RSV infection can significantly alter airway function leading to long-term airway hyperreactivity with subsequent development of asthma later in life. The mechanisms that promote these long-term pulmonary problems are not clear; however, it appears that there may be a genetic predisposition toward the development of a specific immunologic response. The evidence of varied clinical responses to RSV infection supports this contention; i.e. not all children respond in a detrimental way to RSV and most clear the virus without sequelae. This suggests that a particular disease phenotype may be associated with unique mediator responses to RSV in the lung.

Preferential cytokine profiles during viral infections can be observed using inbred mouse strains (96). Recent studies from our own laboratory

indicate that certain strains of mice that differ at the H-2 MHC locus have different cytokine and physiological responses to a primary RSV infection (Table 2). In particular, there appears to be a correlation between airway hyperreactivity (AHR) and IL-13 production, and an inverse correlation between IL-12 and development of AHR. These results tend to follow the responses previously observed in RSV vaccine studies in genetically varied mice. In addition, in human RSV disease there appears to be a correlation between low IL-12 production and severity of the pathophysiologic changes and intensity of the pulmonary inflammation in infants hospitalized for RSV infections. Therefore, the cytokine environment in the lung appears to correlate to disease severity and pathophysiologic outcome. This has been verified in an animal model of RSV-induced AHR in mice that had increased IL-13 production (97). When IL-13 was neutralized there was a significant decrease in the development of AHR, and an associated increase in IL-12 along with a decrease in viral antigen in the lungs. Thus, inappropriate production of IL-13 during RSV infection may lead to a more severe allergic pulmonary response.

Table 2. Primary RSV responses and cytokine environment in lungs of mice are dictated by the MHC genotype.

Mouse strain (MHC)	IL-12	IL-13	Development of AHR*	Exacerbation of allergen response
C57BL/6 (H-2b)	+++	+/–	+	Downregulates
Balb/c (H-2d)	+/–	++	++++	Upregulates
DBA/J (H-2d)	–	+++	+++	Upregulates
CBA/J (H2k)	+	+	++	No change

*AHR, airway hyperreactivity

Asthma is one of the fastest growing diseases in developed countries, especially in young children (98, 99). Asthma-like responses can be induced and/or exacerbated by viral infections that impact lung function through a combination of viral- and inflammation-induced damage (100-106). Recent evidence indicates that cytokines produced during an allergic or infectious response dictate how the pulmonary response will proceed (104, 107). Studies that have coupled RSV infection with allergic responses have clearly indicated that the exacerbation of allergen-induced AHR is associated with RSV-induced IL-5 (104, 108, 109). These latter results correlated to findings from RSV-infected patients with severe respiratory distress who demonstrated increased IL-5 levels (110). In contrast, using a short-term model of RSV infection (4 days), in conjunction with allergen challenge, no increase in Th2 cytokines was observed; however, there was an increase in AHR (111). In additional studies, using a mouse model of long-term RSV infection and allergen sensitization, RSV-induced IL-13 appeared to play a role in the exacerbation of the asthmatic responses (*N.W Lukacs, unpublished data*). In fact, the cytokine environment (IL-12 versus IL-13) developed during the primary RSV infection dictates whether that strain of mouse will

have an exacerbated or regulated asthmatic response (Table 2). Additional studies have demonstrated that the combination of various pulmonary viral infections in murine models of asthma can alter the subsequent airway responses (104, 112-114). Thus, the cytokine response mounted within the lungs during viral infection can dictate the type of immune response (type 1 versus type 2) and the severity of subsequent allergic responses (Figure 1). This concept can also be observed in bacterial infections and CpG oligomers that induce a predominant Th1 response augmenting IL-12 from dendritic cells leading to increased IFN-γ production (115-120).

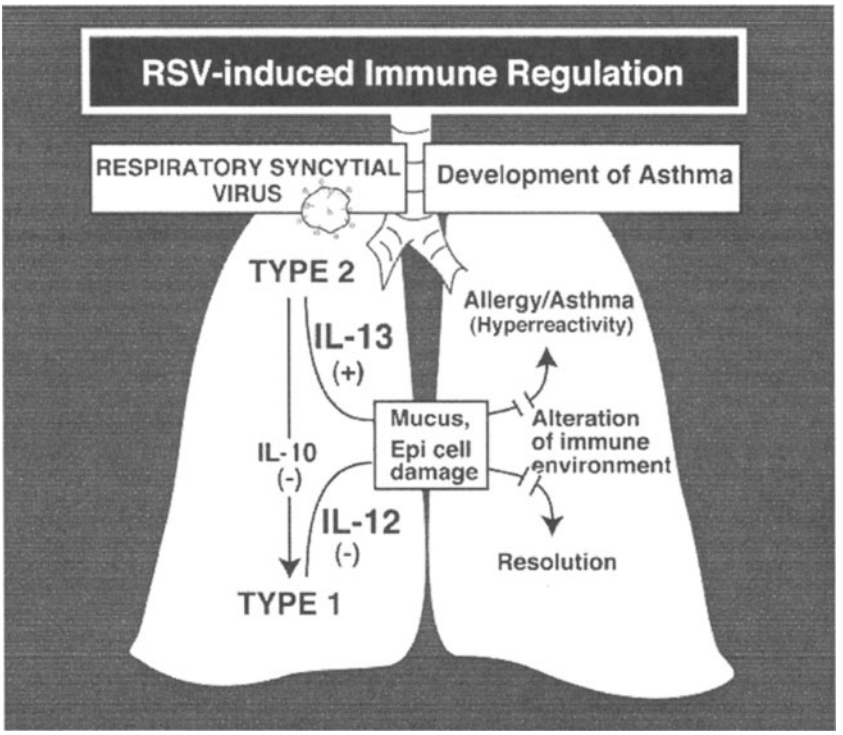

Figure 1. The cytokines produced during a RSV infection can alter the pulmonary environment and dictate the phenotype of subsequent responses to potential allergens. The nature of these responses are likely determined by a number of interacting factors including genetic, environmental, and the infectious agent itself.

Summary

The effective host defense against infections within tissue is reliant on a vigorous inflammatory response including production of cytokines and chemokines leading to the recruitment and activation of neutrophil and monocyte/macrophage populations. These early innate cell responses likely dictate several aspects of the lung responses, including the clearance of the invading pathogen, the intensity of lung pathophysiologic changes and the

development of specific acquired immune responses. The coordination of cytokine production along with cell recruitment and activation becomes critical for the activation of the proper immune responses. Understanding how these interrelated responses develop will aid in determining the viable targets for therapeutic intervention in acute and chronic pulmonary diseases.

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