Review article

Lung inflammatory responses

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Abstract – Inflammation is an important manifestation of respiratory disease in domestic animals.
The respiratory system is mucosal in nature and has specific defense mechanisms used to control
invasion by microbes and environmental elements. Inflammation can be beneficial or detrimental
to the host. This article broadly discusses the primary mediators and mechanisms of inflammation
within the respiratory tract of domestic animals. The role of cells, chemokines, cytokines and
mediators in both acute and chronic inflammation are addressed. The pathogenesis of the initial
insult determines the type of inflammation that will be induced, whether it is acute, chronic or
allergic in origin. Maintenance of the microenvironment of cytokines and chemokines is critical for
pulmonary homeostasis. Uncontrolled inflammation in the respiratory tract can be life threatening
to the animal. The understanding of the mechanisms of inflammation, whether due to microbes or
through inappropriate immune activation such as those occurring with allergies, is required to
develop successful intervention strategies and control respiratory disease in animals.

inflammation / respiratory tract / chemokines / cytokines / disease

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1. INTRODUCTION

Diseases of the respiratory tract are common in domestic animals [1, 6, 17, 31, 62, 76, 84, 87, 103, 108, 140, 141]. Infection and environmental conditions make inflammation a frequent manifestation of respiratory disease. The lungs and upper airways

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are mucosal surfaces commonly exposed to invading pathogens and environmental challenges [74]. As a result, knowledge of the underlying mechanisms of inflammation is important for developing intervention strategies to reduce the impact and damage inflammation causes the host. As with most aspects of immunology, inflammation can be beneficial or detrimental to the host. It is critical that inflammation in the respiratory tract is tightly controlled for the health and well-being of the host. Thus, understanding the causes of inflammation, the mechanisms used to control inflammation by the host, and the mechanisms for damage to the respiratory tract must be considered in order to understand health and disease in the host.

The basic inflammatory response consists of an initiating incident which can be due to a wound, pathogen infection, or an environmental stressor. Any of these initiating factors can result in a sequence of events that induces inflammation and activates the innate and adaptive immune systems. The primary goal of inflammation is to defend the host against infection and repair tissue damage. Non-immune types of inflammation are the result of bacterial or viral products, foreign bodies, or dead and necrotic tissues. Immune inflammation is caused by an inappropriate amplification of mechanisms that also make up the non-immune inflammatory response and thus, the immune system is responsible for the lesions.

The classical features of inflammation include *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain) as discussed in most immunology textbooks. The characteristic manifestations of inflammation become more problematic in the respiratory tract due to the critical nature of its role in oxygen exchange. The three major consequences of inflammation include: vasodilation and reduced blood flow resulting in engorged capillaries; increased capillary permeability allowing fluid and cells to pass into the tissues; and the influx and accumulation of phagocytic and reactive immune cells at the site. Phagocytes take up bacteria and debris in the area, but also release enzymes that damage the tissues, chemokines that attract other cells of the immune system, and cytokines which further increase the inflammation present in the area. All of these events diminish the ability of the lungs to exchange gases, making them life threatening to the host animal.

Inflammatory responses can be categorized as acute and chronic in nature. Each of the inflammatory responses includes a number of mediators that are present in all species of animals; however, they may vary in their responsiveness and reactivity to the various initiating factors. In addition to bacteria and viruses, the environment can produce inflammation in the respiratory tract [34, 47, 65, 69, 101]. Because of the constant exposure to potentially noxious components of the outside air including microbial pathogens, the pulmonary system has developed an extensive defense network of innate and adaptive immune mechanisms to assist in controlling invaders. Inflammatory responses are typically immediate in nature and characterized by changes to the vascular system. In addition, mobile elements such as neutrophils, eosinophils, macrophages and lymphocytes, serum components and various chemokines and cytokines play a role in both causing and controlling inflammation. Intercellular communication occurs using various mediators and messengers that include cytokines, interleukins, leukotrienes, prostaglandins, thromboxane, platelet-activating factor, acute phase proteins, and the various cell adhesion molecules.

This review will divide inflammation in the lungs into acute and chronic forms. The sections will be further divided into describing the cells and mediators involved in each type of inflammatory response and where possible, potential control mechanisms either inherent in the host or as therapeutic interventions that can be important in the control of inflammation. The review will assess the current knowledge of inflammation based on recent and ongoing research and the literature.

2. ACUTE INFLAMMATION

All inflammatory reactions go through an acute phase. The severity, duration and type of response can be variable depending on the initiating factor, the responding mediators and the species of animals. In all species, initiating factors inducing inflammation can be viral, bacterial, mycotic, parasitic or environmental in nature [1, 6, 7, 31, 62, 65, 76, 84, 87, 101, 103, 108, 120, 140, 141]. The nature of the initiating cause will determine the types of cells that respond both acutely and chronically in the inflammatory response. Although all species may share a commonality in their susceptibility to the initiating cause, differences in species due to the environment, housing, activity and potentially genetic susceptibility can play a role in the type and severity of acute lung inflammation [32].

2.1. Initial cellular response

In the first stages of inflammation, neutrophils or eosinophils and mast cells make up the predominant cell type. Inflammation associated with mast cells and eosinophils will be discussed later under allergic responses. Neutrophils enter the lungs in response to the various mediators of acute inflammation [60, 64, 77, 117]. The neutrophils enter into the lung parenchyma primarily from capillaries [49] by binding to up-regulated P- and E-selectins and other cellular adhesion molecules on the surfaces of the vascular endothelial cells [5, 10]. Once neutrophils are present in the lung tissues, the expression of receptors is further increased allowing the various cells to respond to chemokines, further enhancing cell migration to the area of inflammation [88]. A number of molecules and toxins associated with the pathogens, such as lipopolysaccharide (LPS), are also chemotactic for neutrophils [11]. Within hours of the onset of the vascular changes, the neutrophils that have migrated out of the blood vessels begin phagocytizing pathogens

present in the lung parenchyma. Activated neutrophils increase their level of Fc receptor expression allowing the increased uptake of antibody- and complement-coated pathogens [116]. Signals from the activated neutrophils also stimulate the respiratory burst resulting in the production of reactive oxygen and nitrogen intermediates that are active in destroying pathogens [72, 112]. These reactive substances result in further damage to the tissues when the activated neutrophils release their granules into the local tissues. Thus, the exudate present in the lungs in conjunction with infection and acute inflammation consists of dead cells and microbes if present, accumulated fluid and protein substances which can further contribute to the pathology occurring in the lungs.

Simultaneously, and important in the attraction and activation of neutrophils are activated phagocytic cells, especially macrophages [60]. Proinflammatory cytokines produced by activated monocytes/macrophages upregulate the adhesion molecules necessary for neutrophil and monocyte chemotaxis. The cytokines will also induce the monocytic cells to differentiate into macrophages in the tissues [21, 60]. These mediators will be further discussed later in the article. In addition to macrophages, other cell types, such as fibroblasts and airway epithelial cells produce inflammatory mediators and chemotactic factors for neutrophils as well as impacting their activation in the respiratory tract [30, 77].

2.2. Pro-inflammatory cytokines

Cytokines induced in response to inflammation are expressed rapidly and early following injury or infection. The proinflammatory cytokines are predominantly produced by monocytes and macrophages, however, other cell types, such as epithelial cells and fibroblasts are also capable of producing cytokines [30, 60, 77, 90]. Many of these cytokines are important in the development of inflammation within the respiratory tract.

The primary cytokines responsible for acute inflammation include tumor necrosis factor α (TNF), interleukin (IL)-1 (α and β), and IL-6. Along with chemokines, these cytokines often exhibit redundant effects that contribute to inflammation.

Production of TNF is an important manifestation of inflammation and its presence in the respiratory tract results in a wide range of hemodynamic, metabolic and pathological conditions. The most potent inducer of TNF in all species of animals is LPS from gram negative bacteria [28, 61]. Peak TNF levels are observed in bronchoalveolar lavage fluid (BALF) at two hours post experimental inoculation of rats with LPS [70]. TNF is produced primarily from monocytic/phagocytic cells, however, small amounts are produced by other populations of cells as when pulmonary alveolar macrophages are depleted, production of TNF still occurs [14, 51, 97]. Small amounts of inflammation and TNF are important in inducing dendritic cells (DC) and other antigen presenting cells such as macrophages to migrate to the draining lymph nodes, initiating an adaptive immune response [147]. Low levels of TNF also activate macrophages to increase phagocytosis and kill organisms. However, high levels of TNF can be produced in association with a number of virulent pathogens of the respiratory tract including bacteria and viruses. As the levels of TNF increase, severe damage to lung parenchyma and systemic disease can occur resulting in death of the host animal. Individual differences in sensitivity to LPS occurs between species, with horses being extremely sensitive to LPS, which can lead to cardio-pulmonary shock and death [97]. Much of the death associated with bacterial infection, especially due to gram negative organisms, can be attributed to the severe inflammation and septic shock associated with TNF production [38, 127].

A proinflammatory cytokine with many activities similar to TNF is IL-1. IL-1 α and β have interchangeable receptors that are present on many types of cells [78]. Similar to TNF, LPS and other bacterial cell wall components are strong stimuli for IL-1 production [121]. The activity of IL-1 is similar to that observed with TNF, however IL-1 is not as cytotoxic [90]. IL-1 actively induces leukocytes to adhere to endothelial cells and causes cartilage degradation [19, 90].

Following exposure to LPS, TNF and IL-1β are released in the first 30–90 min which in turn activates an inflammatory cascade of mediators that include cytokines, lipid mediators, acute phase proteins, and reactive oxygen radicals, in addition to up-regulating cell adhesion molecules [38].

Production of TNF and IL-1β results in the production of IL-6 from a broad variety of cell types including monocytes/macrophages, endothelial cells, fibroblasts and smooth muscle cells [38]. IL-6 induces the production of acute phase proteins and reduces albumin and transferrin levels [33]. The release of IL-1 and TNF decreases in response to IL-6 production and the influx of inflammatory cells is reduced [2, 110]. An important function of IL-6 includes directing the differentiation of B lymphocytes to immunoglobulin-producing plasma cells which is important in inducing an antigen-specific humoral immune response [89, 123, 133].

Production of TNF, IL-1 α and β, and IL-8 have been extensively studied in relation to respiratory diseases of most species of domestic animals. In some species, such as with the canine respiratory tract, baseline values are currently being established [98]. With the emergence of new technologies, elucidating the relationship between these cytokines and inflammation provides information on their pathogenesis of disease in the lungs and assists in developing successful intervention strategies. In cattle, studies have assessed the role these proinflammatory cytokines, induced by both bacterial and viral pathogens, play in causing inflammation following infection. *Mannheimia haemolytica* is a common cause of pneumonia in cattle. Infection with *M. haemolytica* results in the production of proinflammatory

cytokines in the lungs followed by an influx of neutrophils into the lung parenchyma [135, 136]. This influx of neutrophils is critical to disease control associated with *M. haemolytica*. Reduced numbers of neutrophils entering the respiratory tract, such as observed with concurrent infection with Bovine Herpes Virus-1 increases disease severity significantly [83, 136]. *M. haemolytica* induces the production of the proinflammatory cytokines through a number of mediators including LPS, *M. haemolytica* capsular polysaccharide and *M. haemolytica* leukotoxin, which are released into the intraalveolar exudates [137–139]. Infection with *M. haemolytica* results in the production of IL-1 and TNF in lung tissues [86, 145]. Induction of pneumonia in foals by *Rhodococcus equi* containing a plasmid associated with virulence results in increased TNF and IL-1β production compared to a strain that lacks the plasmid. The results of this study suggest that proinflammatory cytokines are important in organism pathogenicity [56]. In contrast, pigs infected intratracheally with *Actinobacillus pleuropneumoniae*, which also induces an acute pneumonia, have increased levels of IL-1α and β, but do not have increased levels of TNF [15].

Control of inflammation due to excessive proinflammatory cytokine production is critical in respiratory disease. Numerous control strategies have been investigated including the use of steroidal and non-steroidal anti-inflammatory products with varying success. Treatment of pneumonia and the resulting inflammation are reviewed by a number of authors according to species and the reduction of inflammation through the use of anti-inflammatory drugs, antibiotics or depletion of activated cells are common methodologies used [9, 18, 44, 91, 92, 109, 119].

2.3. Chemokines

Chemokines are important mediators of inflammation in the respiratory tract. Chemokines are small polypeptides that control adhesion, chemotaxis, and activation of leukocyte populations. While some chemokines are constitutively expressed, others are either up or downregulated in association with inflammation. Those chemokines active in inflammation are typically produced in response to infection by pathogenic microbes or environmental stressors. As a result of chemokine activation, leukocytes from the various tissue sites migrate into the affected lung tissues. The type of leukocyte attracted by the chemokines is important in defining the type of immune response that occurs. More than 50 chemokines and 15 receptors have been identified in mice and humans to date, with more being identified on an ongoing basis [93]. The ability of a cell to respond to a specific chemokine is based on the receptors on its surface. Thus, depending on the type of infection and the specific chemokines produced, different cells will respond. In addition to neutrophils and eosinophils, resting and active lymphocytes of the different subpopulations express chemokine receptors on their surface. Chemokines are important for the trafficking of the various inflammatory cells to the lungs. Important chemokines in acute respiratory inflammation include CXCL8, also known as interleukin (IL)-8, and CXCL1, 2 and 3, all which attract and activate neutrophils [8]. The CXC chemokines have been studied in domestic animals [85]. In addition, there is a great deal of interest in understanding the activation of CXCL8 due to its ability to recruit and activate leukocytes, especially neutrophils to areas of inflammation [1, 15, 16, 51, 86]. Exposure of porcine alveolar macrophages to LPS induces rapid and prolonged production of this chemokine, however, low levels of the proinflammatory cytokine, TNF, are also required [79]. A number of bacteria have been shown to induce CXCL8 production in host species including *Mycoplasma hyopneumoniae, M. haemolytica, A. pleuropneumoniae,* and swine influenza virus [1, 16, 126, 131, 132]. In addition, LPS is a potent inducer of

CXCL8 [63]. Other chemokines such as CCL2, 3, 4 and 11 have similar functions with monocytes, macrophages, or eosinophils, but less is known about their role in respiratory inflammation in domestic animal species [23]. Research has been performed to investigate the use of anti-CXCL-8 antibodies as an intervention strategy to block neutrophilic infiltration into lung tissues. This study used pigs as a model, but found that topical anti-CXCL-8 treatment after lung injury increased CXCL-8 production and decreased lung function, suggesting that CXCL-8 alone is not the only chemoattractant for neutrophils inducing lung damage [7].

2.4. Serum proteins

A number of serum proteins are actively involved in acute inflammation reactions. These systems include the complement, coagulation and kinin systems as well as the acute-phase proteins. Deposition of immunoglobulin immune complexes in the lungs results in the activation of complement [60]. The complement system consists of approximately 20 serum proteins. Vascular changes occur due to the indirect effect of the anaphylatoxins (C3a, C4a, and C5a). The anaphylatoxins cause the separation of vascular endothelial cells to increase cellular migration from blood to tissue, induce the degranulation of mast cells and histamine release resulting in escalation and enhancement of inflammation through vasodilation and smooth-muscle contraction. Activation of complement is important for controlling pathogens through opsonization and formation of the membrane attack complex. Complement activation has been shown to be required for control of bacterial infections or the respiratory tract such as pneumococcal pneumonia [71].

Activation of the complement system occurs through the activation of the classic, alternative or mannose-binding pathways, each with a different mechanism of initiation. However, activation of complement in the respiratory system can result in severe lung injury [41]. In addition to affecting the vascular system, the anaphylatoxins of the complement system induce leukocytes to adhere to vessels, and extravasate through the vessel wall and migrate to the site of inflammation/infection [60]. It has been shown that mice deficient in the C5a receptor have a pronounced reduction in lung injury following deposition of immune complexes in the lungs [27]. Damage to the blood vessels in the region by the chemical mediators produced by the complement system activates the coagulation system resulting in thrombin acting on fibrinogen to produce fibrin and fibrinopeptides which form clots to prevent the spread of infection. Formation of clots in the respiratory system can be life threatening. Removal of the formed clots is achieved by the fibrinolytic system, resulting in the production of plasmin, which break the fibrin strands [73]. Plasmin also activates the classical complement pathway. With the continued activation of complement, the level of inflammation escalates resulting in further tissue damage. If this cycle is allowed to continue, severe respiratory disease develops which can result in the death of the host. As a result, control of complement activation systems is critical for the recovery of the animal from clinical disease. Because of the complement systems inherent ability to cause tissue damage, many control mechanisms are in place. However, while these control mechanisms are successful much of the time, occasionally the inflammatory process and control of the complement cascade is lost and death of the host animal can occur.

Macrophages within the respiratory system are important in metabolizing exogenous arachidonic acid to its inflammatory metabolites via the lipoxygenase and cyclooxygenase pathways resulting in the production of prostaglandin, thromboxane, and leukotrienes [20]. Arachidonic acid is derived from membrane phopholipids from various cell populations present early in the inflammatory process. Depending on the cell type

affected, the different prostaglandins produced result in diverse physiological effects including increased vascular permeability and dilation, and attraction of neutrophils and can even be beneficial [134]. Arachidonic acid is also metabolized by the lipooxygenase pathway to yield the leukotrienes, of which there are four. Three of the leukotrienes, LTC4, LTD4, and LTE4, make up the slow-reacting substances of anaphylaxis (SRS-A) which induce smooth muscle contraction [69]. It has been demonstrated that arachidonic acids and prostaglandins play a role in lung injury induced by LPS [4].

One important class of serum proteins produced in response to tissue damage and inflammation is the acute-phase proteins. Production of acute phase proteins is a dynamic process involving both systemic and metabolic changes and provide nonspecific protection early following infection [122]. These proteins are typically produced in the liver and are present in the serum. One common protein is the C-reactive protein which binds to the C-polysaccharide cell-wall component of bacteria and fungi. The binding of C-reactive protein to a pathogen results in activation of the complement cascade which increases their uptake by phagocytic cells. Other acute phase proteins include haptoglobin, and serum amyloid A (SAA). Increased levels of a number of these acute phase proteins have been associated with respiratory diseases of domestic animals [39, 66, 68, 113, 143, 144]. An excellent review of the application of the acute phase proteins in veterinary clinical chemistry is available [99]. The use of acute phase proteins is more controversial in human medicine, where it has been demonstrated that measuring C reactive protein is not sensitive enough to assess respiratory health [129]. Induction of acute phase proteins in APP-induced pneumonia was confirmed by demonstrating that effective antibiotic treatment reduces inflammation and lowers levels of acute phase proteins [94].

3. CHRONIC INFLAMMATION

Chronic inflammation initially follows the same pathway as an acute inflammatory response. Chronic inflammation occurs if the acute inflammatory response is inadequate to clear the tissue of invading microbes or substances. Typically, infections are successfully resolved through the elimination of the causative organism. Examples of pathogens that induce chronic inflammation in the respiratory tract include *Mycoplasma hyopneumoniae* and porcine reproductive and respiratory syndrome virus (PRRSV) in pigs, respiratory syncytial virus (RSV) in cattle and the various mycobacterium species in most animals [46, 107, 142]. Allergic responses also tend to induce chronic inflammation in the respiratory tract and this will be discussed in a separate section below. The underlying purpose of chronic inflammation is to clear necrotic debris produced during the acute inflammatory process, to provide defense against persistent infections, and to heal and repair the damage to the lung parenchyma. Destruction of the normal tissue architecture results in scarring, which can be problematic in the respiratory tract due to reduced area for oxygen exchange.

3.1. Cells of chronic inflammation

The cells of chronic inflammation include lymphocytes, macrophages and plasma cells all of which are monocytic cells. Additional macrophages begin arriving in the lungs approximately 5–6 h after the inflammatory process has begun. Upon arrival, the macrophages become activated with increased phagocytic capabilities and produce a number of mediators and cytokines that further contribute to the inflammatory response. Monocytes are attracted by many of the same chemotactic agents that attract neutrophils as well as the CCL chemokines [55]. Chemokines and cytokines are produced by the mononuclear cells in response to tissue breakdown products. The monocytes adhere to the endothelial cells via

selectins and integrins, similar to neutrophils and migrate through the vessel walls. Once monocytes reach the area of inflammation, they become activated and begin phagocytizing bacteria and damaged cells, including neutrophils and fibrin deposits and tissues. Collagenases and elastases are released from the macrophages that destroy connective tissue [22]. A plasminogen activator is released, resulting in the production of plasmin and the tissue matrix relaxes [73]. Simultaneously, macrophages secrete IL-1 which attracts and activates fibroblast proliferation and collagen synthesis [146]. The new tissue replaces the damaged tissue and gradually remodelling occurs until the tissues in the area of inflammation return to normal.

Typically, inflammation is considered beneficial to the host and necessary to eliminate and prevent the colonization of invading microbes, to activate the innate and adaptive immune responses, as well as to contribute to the healing process. If, however, the inflammatory process is not controlled or fails to resolve the infection or clear the noxious stimulus, protracted and increased local cell injury and trauma occurs. As the reaction continues, additional inflammatory cells are attracted and activated resulting in the release of more mediators. As this process continues, the response becomes chronic in nature [106]. The ability of the respiratory tract to return to normal depends on the cause, duration, and how successful the inflammatory and immune responses were in clearing the lungs of the stimulus. If the inflammation and resulting immune response are successful in eliminating the pathogen, the inflammatory response resolves and the lung tissue returns to normal. However, if the offending microbe cannot be destroyed or if the cause of the inflammation is an inappropriate response to stimulus, such as with some allergic types of reactions, the inflammatory process persists.

Depending on the initiating cause, granulation and granulomas may be formed, while in other cases, fibrosis, bronchial smooth muscle hypertrophy and bronchoconstriction occur [111]. These changes and the resulting damage to lung parenchyma become increasingly important as air exchange space becomes compromised, emphysema occurs, fluid and cells accumulate and oxygen exchange is reduced.

3.2. Cytokines associated with chronic inflammation

The same proinflammatory cytokines associated with acute inflammatory disease of the respiratory tract are active in chronic infections. However, the levels of these cytokines remain persistent and in excess in production [45]. A number of respiratory pathogens induce the long term production of TNF and IL-1, which results in chronic pneumonia. *Mycoplasma hyopneumoniae*, a common bacteria that infects pigs, induces significant levels of the proinflammatory cytokines, IL-1, IL-6 and TNF long term [12, 13, 125, 126]. Increased levels of these cytokines may play a role in the potentiation of pneumonia produced in pigs infected with both *M. hyopneumoniae* and PRRSV [126]. Over time, the release of IL-1 and TNF decreases in response to IL-6 production and the influx of inflammatory cells is reduced [2, 110]. An important function of IL-6 is the induction of differentiation of B lymphocytes to immunoglobulin-producing plasma cells which allows the respiratory tract to begin clearing the microbes from the lungs [89].

Resolution of chronic pneumonia will be successful if the initiating cause is eliminated or resolved. With some organisms, such as with mycobacterial infections, inflammation is controlled through the formation of abscesses which isolate the organism from spreading throughout the body. However, with the formation of abscesses, air space can be compromised resulting in reduced ability for air exchange and poor production. Additionally, chronic respiratory tract can reduce production parameters for food animals resulting in

economic loss to the producers. This is especially problematic to the swine industry where chronic pneumonia due to combined respiratory pathogens is common [124]. One of the most common causes of chronic inflammation in the respiratory tract is allergic reactions.

4. INFLAMMATION IN THE PORCINE RESPIRATORY DISEASE COMPLEX

An example of the importance of inflammation in the respiratory tract is observed in swine production. Respiratory disease remains a significant problem for swine producers throughout the world in spite of intensive disease reduction strategies. Respiratory disease associated with multiple pathogens characterized by slow growth, decreased feed efficiency, anorexia, fever, cough and dyspnea has been termed the porcine respiratory disease complex (PRDC). The respiratory disease associated with PRDC is the result of numerous pathogens. However, at the Iowa State University Veterinary Diagnostic Laboratory, PRRSV remains the most common pathogen isolated from pigs with clinical disease compatible with PRDC. Other common pathogens include swine influenza virus (SIV), *Pasteurella multocida, M. hyopneumoniae*, and porcine circovirus type 2 (PCV2). Other bacteria include *Haemophilus parasuis, Streptococcus suis*, and *Actinobacillus pleuropneumoniae* (APP). Together, the interaction of these pathogens and the inflammation they produce result in significant economic loss to the swine industry throughout the world [124]. The combination of pathogens that cause acute inflammation such as swine influenza virus (SIV), combined with pathogens that persist in the host makes controlling this complex disease challenging. Infection with APP in pigs, causes severe inflammation within the respiratory tract and in addition can cause systemic disease due to septicemia [15]. Similarly, SIV induces a significant inflammatory response in the respiratory tract following infection, which may play a role in the rapid clearance of the virus from the host [131]. In contrast, infection with PRRSV, while systemic in nature and capable of inducing significant interstitial pneumonia, does not appear to produce significant levels of proinflammatory types of cytokines and inflammation [130]. The lack of significant inflammation associated with PRRSV may be one reason the virus persists in the host for long periods of time [131, 142]. These examples demonstrate that in the swine, while a certain level of inflammation within the respiratory tract is necessary to clear the pathogen from the host, some pathogens can modulate the system to allow their survival in the host.

5. ALLERGIC REACTIONS AS A CAUSE OF INFLAMMATION IN THE LUNGS

Inappropriate inflammatory responses in the respiratory tract are often associated with allergic responses to antigens [36, 37, 50, 52, 81, 96]. In allergic reactions, neutrophils, macrophages, lymphocytes, mast cells and eosinophils can all play important roles in causing disease [29, 37, 53, 100]. Mast cells containing granules made up of a mixture of chemical mediators, including histamine, are located in the mucosal and submucosal tissues near small blood vessels and postcapillary venules [29]. In these locations, they guard against invading pathogens. Mast cells are activated by the binding of surface receptors to IgE or IgG [35]. In order to prevent indiscriminate mast cell degranulation, the bound IgE must be crosslinked by multivalent antigens. Upon activation, the mast cells release their granules and secrete lipid inflammatory mediators, such as prostaglandin D_2 and leukotriene C4, and cytokines, such as IL-1 and TNF [32, 40, 67, 75]. Release of these mediators initiates a local inflammatory response.

Histamine released by the mast cells increases blood flow and vascular permeability that leads to fluid and blood protein accumulation in the alveoli. As a result, the gas exchange can be severely compromised. Eosinophils are also actively involved in allergic responses in the lungs. The activation and degranulation of eosinophils is strictly regulated, since inappropriate activation, as with mast cells is harmful to the host. Release of IL-4 by T lymphocytes increases the number of eosinophils released from the bone marrow into the circulation [82]. Eotaxin 1 (CCL11), 2 (CCL24) and 3 (CCL26) are chemotactic for eosinophils [104].

Epithelial cell-produced factors are linked to the pathogenesis of allergic responses such as asthma. In addition, factors produced by epithelial cells under pathological conditions drive DC in the lungs to produce a strong, often inappropriate T_H2 response [3, 118]. Expression of CCL17 (thymus and activation-regulated chemokine) and CCL22 (macrophage-derived chemokine) on the surface of DC appears to selectively attract T_H2 cells [118]. The interaction between epithelial cells and DC is important for inducing and controlling allergy-induced inflammation in the respiratory tract. Additional studies are needed to investigate these responses in multiple species of animals as well as in vivo. Many of the antigens involved with allergic reactions are small proteins that are typically inhaled. On contact with the mucosa of the respiratory tract, the soluble proteins diffuse into the tissues. Depending on the host, the reaction that results can be life threatening. Understanding the impact the environment plays in respiratory health and disease of both production and companion animals becomes critical in assessing the roles that inflammation caused by allergic reactions to microparticles and antigens play in respiratory disease [34, 48, 65].

In an allergic reaction, degranulation of mast cells and T_H2 activation cause eosinophils and neutrophils and other leukocytes to accumulate and become activated leading to severe inflammation of the airways. Chronic inflammation of the airways is often characterized by the continued presence of increased numbers of T_H2 type lymphocytes, eosinophils, neutrophils, and other leukocytes [40]. The respiratory tract has a predominantly T_H2-type of microenvironment to reduce inflammation and maintain homeostasis; however, the relationship between T_H1- and T_H2-types of responses is not well characterized and is not a static condition [95]. The increased numbers of leukocytes and inflammatory cells, including fibroblasts result in remodelling and narrowing of the airways and increased mucin production. The action of other T_H2-type cytokines including IL-9; result in mucus production by goblet cells [67]. Many of the changes in the lung parenchyma are due to the involvement of eosinophils. Chronic inflammation due to these types of immune responses occurs in cats in the form of feline bronchopulmonary disease, horses with heaves and cattle with hypersensitivity pneumonitis [50]. These disorders are all characterized by alveolitis, vasculitis and fluid exudates in the alveolar spaces. The alveolar septa become thickened and the lesions are infiltrated with inflammatory cells, most of which are eosinophils and lymphocytes. With long term exposure to hay dust, horses may develop chronic obstructive pulmonary disease (COPD) [43]. In addition to hay dust, fungal extracts often appear to be involved in the development of this chronic respiratory disease. Affected animals have large numbers of neutrophils, eosinophils and lymphocytes in the small bronchioles. The cytokines, IL-4 and IL-13, are required for differentiation into T_H2 lymphocytes and for isotype switching by B cells to IgE antibody production [40]. Proliferation of granulocyte prognitors, primarily eosinophils in the bone marrow are promoted by the T_H2 cytokine, IL-5. Interestingly, despite years of previous antigenic stimulation, there was no polarization of lymphocytes to a T_H2-type of response in horses with COPD during

clinical remission [40]. Typically, neutrophils are recruited to the lungs of horses with COPD and further add to the inflammatory process [24, 57, 128]. There is evidence that T_H2 cytokines are involved in the modulation of the inflammation from a neutrophilic to an eosinophil-induced type of inflammation [24, 57]. Functional IL-4 receptors are present on human neutrophils and their activation leads to protein synthesis and inhibition of apoptosis [58]. In addition, IL-4 stimulates neutrophil phagocytic activities and bactericidal capabilities [24]. Interestingly, although the respiratory reaction of COPD horses is triggered by dust and the environment, eosinophils are not always predominant in the respiratory tract, but often a neutrophilia is present. As a result, this type of reaction differs from the allergic reactions and asthma associated with humans. Little is known about the inducers of allergic reactions in the respiratory tract of domestic animals, including predisposing factors and even disease manifestations.

6. REGULATION OF INFLAMMATION IN THE LUNGS

Because inflammation can quickly become life threatening in the lungs, protective measures are in place for protection and control. In addition to inducing inflammation, cytokines produced by lymphocytes play an active role in the respiratory tract by downregulating the production of the inflammatory cytokines and immune response. Cytokines such as IL-10 and TGF-β are important in modulating the inflammatory and immune responses in the lung [54, 102, 114, 115]. As a result, while inflammation is induced to activate the immune system and control pathogens, modulation occurs through the induction of other cytokines. Research has demonstrated that the respiratory tract maintains an environment that tends to decrease inflammation [105]. The production of a wide range of inflammatory cytokines from monocytes and pulmonary

macrophages are inhibited by IL-10 [80]. Deficiencies in IL-10 in the respiratory tract are associated with increased tissue injury and inflammation [105]. The importance of cytokines such as IL-10 is demonstrated by the fact that IL-10 levels are decreased in the bronchoalveolar lavage fluid of patients with asthma and acute respiratory distress syndrome [25, 26, 59]. The regulation of proinflammatory cytokine production by macrophages in the lungs is under investigation and research has shown that there are differences in cytokine production and regulation between monocytes and macrophages [90]. These differences are demonstrated by IL-4 suppressing IL-1-β and TNF production in LPS stimulated monocytes, but not in LPS stimulated pulmonary alveolar macrophages [42]. Thus, the cytokines produced by phagocytic cells are influenced by their phenotype, the initiating stimulant, location, and possibly animal species.

7. CONCLUSIONS

In summary, inflammation in the respiratory tract plays a significant role in the diseases of domestic production and companion animals. Inflammation can be acute or chronic depending on the initiating factor and the response induced by the host. A number of proteins and cascades have the potential to be activated depending on the cause of the inflammation, the ability of the host to respond and the type of response that occurs. Understanding the pathogenesis of the initial insult provides valuable information on the type of response that will occur, whether it is a chronic inflammatory response and pneumonia due to a pathogen such as *Mycobacterium* sp., or an allergic response as observed with equine COPD and heaves. Other initiating factors such as gram negative bacteria and viral infections, alone or combined, can result in acute inflammation of varying severities. Due to the importance of maintaining pulmonary homeostasis, regulating cytokines and immune responses are critical. Much of

these processes are currently being elucidated, however, it appears that cytokines such as IL-10 and TGF-β, with anti-inflammatory capabilities are critical in controlling inflammation in the respiratory tract. More information is needed on the various inflammatory processes of the respiratory system of domestic animals due to the importance of respiratory disease in veterinary medicine.

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