Animal and Veterinary Sciences
2022; 10(2): 15-20
http://www.sciencepublishinggroup.com/j/avs
doi: 10.11648/j.avs.20221002.11
ISSN: 2328-5842 (Print); ISSN: 2328-5850 (Online)

Review on Immunity to Fungal Infections in Animals

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To cite this article:
Dessie Abera. Review on Immunity to Fungal Infections in Animals. *Animal and Veterinary Sciences.* Vol. 10, No. 2, 2022, pp. 15-20.
doi: 10.11648/j.avs.20221002.11

Received: February 22, 2022; **Accepted**: March 25, 2022; **Published**: March 31, 2022

Abstract: The occurrence of mycosis is relatively uncommon in healthy and immunocompetent hosts. But now a days, the incidence of fungal infections are increasing and there is no effective vaccine for fungal infections in contrast to bacterial and viral diseases. And also, available antifungal drugs are not effective to treat infected animals. Understanding the immunity against fungal infections is of interest which can contribute more for therapeutic and vaccine development. Therefore, this review focuses on the immune components involved in clearing fungal pathogens. Disease outcome is a result of host-pathogen interactions. Immunity is the body's resistance to infection. Innate and acquired immune systems are involved to eliminate animal fungal infections. Innate immunity is not specific. It is the first line of defense, with genetically encoded receptors that identify greatly conserved pathogen-associated molecular patterns. Physical barriers, phagocytic cells, chemotactic factors and natural killer cells are some of the innate defense mechanisms. Adaptive immunity is specific. Lymphocytes have a unique and specific antigen receptor. It can be a humoral or cellular type of immune system. In adaptive immunity, there is a development of immunological memory in the host after exposure to a pathogen. However, there are no effective vaccines and antifungal drugs. So it causes high morbidity and mortality in animals and fungal pathogens have become a significant clinical challenge, leading to a global threat to controlling fungal infections. Therefore, good management of animals and treating concurrent infections strengthens their immunity. Besides, promoting research into fungal infections to develop new diagnostics, anti-fungal drugs and vaccines are recommended.

Keywords: Fungi, Immunity, Infection, Mycosis

1. Introduction

Mycosis is an important disease caused by fungi. The fungi crosses the drug-resistance barriers and establish infection in animals [1]. There are many fungal species across the globe and most of them are widely spread in the surrounding, as well as in humans and animals normal flora [2]. Fungi are classified in two forms based on their morphology. Yeasts are single-celled organisms that reproduce asexually through the formation of conidia, whereas hyphae are multicellular organisms with branching tubular filaments and various cell wall compositions. The hyphal and conidial morphotypes are associated with tissue invasion and colonization respectively [3].

It is very difficult to diagnose, treat and eradicate fungal diseases compared to bacterial infections and also vaccine availability against the disease is limited [1]. The incidence of fungal infections are increasing. Fungal diseases threaten animals, plants and humans, so it is a problem of great concern to scientists in all disciplines [4]. Fungal infections occur rarely in a healthy and immunocompetent hosts, even though they are exposed to infectious pathogens. But number of animals suffered by fungal diseases are increasing in the previous twenty years. It may originate from fungi that are either opportunistic or pathogenic [5]. A disease occurrence is depend on the interaction between fungal pathogenicity and host resistance [1]. For example, immune system of the host and dermatophyte virulence factors are essential for the disease, dermatophytosis occurrence in companion animals. The host immune reaction are initiated through glycopeptide and keratinase virulence factors [6].

Animals need to keep away from becoming a free meal to microbes [7]. Immunity is the resistance of a host to infection. Defense mechanisms of immune systems against fungi are classified into two broad categories. They are innate immunity and adaptive immunity [8]. The cell wall of fungi consists of polysaccharide and lipid residues that initiate the

immune response [9]. Innate immunities are common for all animals. It depends upon genetically encoded receptors and they recognize highly conserved pathogen-associated molecular patterns. Whereas adaptive immunities are unique for vertebrates and are mediated through lymphocytes having a specific antigen receptor [8]. These immune systems are normally powerful due to the fact that most fungi do not cause disease in the environment. Many critical fungal diseases occur in immunosuppressed mammals indicating their immune systems effectiveness against fungi [10].

According to immune response induction methods, adaptive immunity classified into two main areas. They are humoral and cellular immune systems. Immunoglobulins play a great role in humoral immune system which are produced by B lymphocytes. But in cellular immune system, T lymphocytes are involved. It is based on major histocompatibility complex (MHC)–restricted antigen presentation to the T cell receptor on T lymphocytes [8]. Fungal pathogens of humans can also cause major animal infections. For example systemic animal mycosis include: Aspergillosis, Mucormycosis, Candidiasis, Cryptococcosis, Coccidioidomycosis, Histoplasmosis, Paracoccidioidomycosis, and Blastomycosis. Many antifungal drugs are utilized in the remedy of fungal diseases. But now a days there is a report of antifungal resistance development [5]. And fungal pathogens in animals are a significant clinical challenge. Control of fungal diseases has become a global challenge due to the absence of standardized diagnostic tools, effective vaccines and antifungal drugs [2]. Therefore, understanding immunity and the immune components involved against fungal infections will contribute more for therapeutic and vaccine development against fungal diseases.

2. Innate Immunity

The innate immune system protects the host in their lifespan from pathogens [7]. This defense system is basic for the survival and reproduction of all multicellular organisms [11]. Animals, including insects, have an innate immune system, which protect them from the majority of pathogens they encounter [7]. Innate immunity, in contrast to adaptive immunity, offers an inherent and generic protection of the host from infection. It is found almost in all animals so that they can survive in their natural habitat in the face of potential pathogens. Before the appearance of lymphocytes, innate immunity is believed to have evolved [8]. Innate immunity in the host immune system serve as a first line of protection. However, now a days it attracted attention because, it can distinguish self from non-self and activates adaptive immune mechanisms through the delivery of specialized signals [1].

The inherent immune components of the host can quickly detect infections through coded germ line receptors. It detects a set of molecular patterns that are conserved across a wide range of microbial species. Although Toll-like receptors (TLRs) function against fungal pathogens are not well known, they have been investigated in the defense against *A. fumigatus*, *C. albicans*, *C. neoformans*, *Pneumocystis* and *Coccidioides* [1]. Animals' innate immune systems detects a set of overlapping conserved genetic patterns associated with microorganisms (MAMPs). In animals and insects, MAMP subgroups are directly or indirectly recognized by pattern-recognition receptors (PRRs). PRRs are named Toll receptors and TLRs in insects and vertebrates respectively. In fungal infections, these receptors aid immunity by binding chitin molecules [7]. Therefore, we will see a number of relatively nonspecific antifungal defense mechanisms in animals which can establish an immunity against fungal infection in the following sections.

2.1. Physical Barriers Against Fungal Infection

Physical barriers are the first defensive systems in the innate immunity that separates the host from the surroundings. Some of the barriers include the skin and mucous membranes of the respiratory, gastrointestinal and genitourinary tracts [1].

2.1.1. Skin and Mucous Membranes

Antimicrobial compounds are present on the surface of these physical barriers. The antimicrobial agents are produced and secreted by epithelial and endothelial cells. Skin and mucous membranes also have a commensal microflora which have a role in preventing colonization by pathogenic microorganisms [1]. Innate immunity relies on the skin as a physical barrier against possible infections, as well as in specific immune defense mechanisms [12].

2.1.2. Immunity and Commensal MICROBIAL Communities

The innate immune system is critical for microbial community structure and for protecting the host by preventing colonization by pathogenic fungi and controlling commensals from turning into pathogens (Blanco and Garcia, 2008; Rivera, 2014).

2.2. Phagocytic Cells

During fungal infections, once the fungal pathogen have passed a series of innate mechanisms of defense like physical barriers, and cellular membranes, they encounter with cellular receptors and various humoral components. The host defense system involve phagocytic cells such as neutrophils, dendritic cells, monocytes, and macrophages as well as natural killer cells, epithelial, and endothelial cells [1]. PMNs (polymorphonuclear leucocytes) reduce the quantity of effective fungal inoculum to which an animal is exposed, lowering the likelihood of fungal infection development. PMN-based resistance was also observed in guinea pigs through inoculation of *C. albicans* on the skin and then complement was activated. Thus, *C. albicans* was removed through infiltration of PMN at the epidermis of the skin. *Aspergillus* spores are also killed by the macrophages. But PMN plays a great role in protection of the host against hyphae [13].

The host defense mechanisms can adapt to various types of fungal infections. The primary defense cells involved in fungal killing of *Cryptococcus* and *Pneumocystis* infections are macrophages. But the first line defense cell in *Aspergillus fumigatus* and *Candida albicans* infections are neutrophils. Pathogen-associated molecular patterns (PAMPs) are molecular structures shared by many groups of microbial pathogens. They are recognized by pattern recognition receptors (PRRs). These receptors are available in various host cells like monocytes, macrophages, dendritic cells, B-cells, T-cells and endothelial cells. TLRs are also included in PRRs and they are cellular receptors that detect microbial pathogens and initiate subsequent inflammatory reactions for chemotactic factor synthesis in vertebrates [1]. Inflammatory cytokines play a great role in *Aspergillus fumigatus* infected mice. *A. fumigatus* was cleared through alveolar macrophages and recruited neutrophils. Recovery was facilitated through removal of cellular and fungal debris by recruited monocytes [14].

2.3. Complement Activation

Recruitment of leukocytes through chemotactic factors is a critical point in the defense system of the host. During fungal infection there are various chemotactic factors produced at the site of infection. They include peptides, leukotrienes and fungi products. Chemokines are secreted by many types of host cells after initiation with cytokines or microbial products. Host cells involved in production of chemokines are leukocytes, epithelial cells, endothelial cells, fibroblasts and smooth muscle cells. In addition to chemotaxis, chemokines also regulate many biological activities, like hematopoiesis, angiogenesis, cytokine induction, antigen presentation and Th cell differentiation. These immune activities play a great role in protection of the host from acute and chronic fungal infections [1].

Complement activity and complement components (C3 and C4) were involved in immune response of German shepherd dogs when infected with systemic Aspergillosis disease [15]. Using the model of experimental dermatophytosis of guinea pigs, leukocyte chemotaxis occurred due to complement activation as well as to release fungus-derived chemotactic factors [16]. *A. fumigatus* was cleared from mice by tumor necrosis factor- α, interleukin (IL)-6, and IL-1β. Recruited monocytes were participated to remove the cellular and pathogen debris. Inflammatory cells like cytokine production were rapidly decreased, and pneumonia self-healed facilitated; in addition to alveolar macrophages and recruited neutrophils (PMNL) action for the recovery [14].

Extracellular killing

In fungal infections, natural killer (NK) cells reduce the quantity of effective inoculum to which an animal is exposed, and so lowering the occurrence of fungal disease [13]. NK cells of lymphoid cells from non-immune animals played a significant role in the laboratory for killing of *Cryptococci* as a first line of defense. However, this protection seems to reduce only the quantity of effective fungal pathogens inoculum and T-cell-mediated immune reactions required to prevent fungal disease development [13].

3. Adaptive Immunity

Recognition of a pathogen through a unique antigen receptor of lymphocytes are required for effective adaptive immune response [8]. Adaptive immunity is very essential in the defense of infections since it is specific. And the host will have an immunological memory after exposure to a specific infectious pathogen but it is available only in vertebrate animals [7]. Investigations conducted in naturally dermatophytosis infected cats showed the significant role of cell-mediated and humoral immune responses [17]. However, in other studies, immune reactions to dermatophyte infection mainly depend on cell mediated immune (CMI) than humoral immune responses of the animal [18]. Dermatophytosis immunization has been successful with the whole mycelium. It can be injected intra or subcutaneously. The immunity developed was higher in the immunized part of the body than other parts and it was accompanied by cutaneous sensitization [19].

Establishment of an effective immunity in livestock and companion animals through immunological reactions in naturally infected animals or experimental immunizations have been studied extensively. Experimental immunizations can be done with the whole cell, culture filtrate or purified antigenic preparations [20]. In dermatophyte infected cats, immunity to infection has been determined to be a relative. Immunity level can be overcome by exposure of a cat by a large enough dose of *Microsporum canis*. Direct application of a large number of spores in a traumatised skin can result a much more severe challenge than a naive cat exposed to an infected cat in a cattery [21].

3.1. Humoral Immunity

Toll-like receptors and other PRRs contribute in the PAMP detection and their signal activates production and secretion of proinflammatory cytokines. These molecules induce the expression of costimulatory chemicals to promote the initiation of adaptive immunity in the antigen presentation process. A single infectious fungal pathogen can simultaneously activate many PRRs which endows the immune system with various probabilities for an effective and proper immune response [1]. Fungal infection can be prevented through resistance development in cattle. It can be investigated by experimental infections of cattle by *T. verrucosum*. Infection cured spontaneously in the first challenge of cattle and then they became resistant to cutaneous reinfection [19]. The calves were experimentally infected with *T. verrucosum* and humoral response was first observed on day 33. There was an influx of B cells and Gold staining of protein G-colloidal indicates the presence of immunoglobulins in the dermis and epidermal layers. Serum antibodies specific to Trichophyton were appeared between days 33 and 55 [18].

It is possible to produce agglutinins, precipitins, and

complement-fixing antibodies from animals immunized by killed dermatophytes [19]. Cats developed high titres of IgG against dermatophyte but small level of cell-mediated reaction occurred against *Microsporum canis* of dermatophytosis in cats [21]. In dermatophytosis infected cats and dogs, the role of adaptive immunity is not clear. However, antibodies by opsonisation and complement activation could have an antifungal effect [22]. In naturally occurring feline dermatophytosis caused by *Microsporum canis,* anti-dermatophyte antibody assays indicate that cats are found to be with high titre of IgG and lgM [23].

The immunohistochemical findings of dogs with nasal Aspergillosis suggest that there is an active immunological response to nasal cavity infection by *A. fumigatus*. The main humoral immunological results were found to be predominant in IgG than IgA and IgM plasma cells [24]. Disseminated Aspergillosis was performed on a four year old German shepherd female dog and specific polyclonal immunoglobulins such as IgG, IgM and IgA were involved in the protection [25]. IgA predominance was detected in dogs with disseminated Aspergillosis than another immunoglobulin groups. They bind to fungal hyphae within the granulomas of tissues and they are particularly found in deep tissues since IgA is mainly secreted in submucosal areas that serve as a mucosal barrier [26].

In the animal Cryptococcosis, IgG antibody against a capsule is detected from most sera samples and it plays an important role to protect the host [13]. Circulating complement-fixing antibodies to M. lanosum were first demonstrated from the serum of a dog having a natural cutaneous infection and are important for protection of dogs [19].

3.2. Cellular Immunity

Cell-mediated immune response is very important in the elimination of fungal elements, but it doesn't mean anti-fungal antibodies have no contribution. In the experimental *Microsporum canis* infection of cats, an association was detected between onset of fungal disease occurrence and level of lymphocyte proliferation. In the increased cell-mediated lymphocyte reactions, the occurrence of fungal disease were reduced compared to humoral immune response. But in guinea-pigs and mice, experimentally infected with dermatophytosis, lymphocyte proliferation was suppressed [18]. T cell-mediated immune response is important for the recovery of skin and mucosal infections like candida and dermatophyte fungal pathogens. And for systemic fungal pathogens like cryptococcus and histoplasma. Chronic fungal infections are usually related to immunosuppression or lack of T-cells against infectious fungal antigens [13].

The immunological findings of dogs with nasal Aspergillosis, caused by *A. fumigatus* is complement aid phagocytosis by PMNs and macrophages [13]. Many macrophages and dendritic cells expressed MHC class II molecules, and a mix of $CD4^+$ and $CD8^+$ T cells. Their cell-mediated immune responses are primarly Th1-regulated. Therefore, antigen-presenting cells such as macrophages and dendritic cells, as well as T lymphocytes, were involved in the immune response [24]. Invasive Pulmonary Aspergillosis in mice indicates that existence of Aspergillus antigens inducing the development of protective Th1 and Th2-type reactivity during infection [27].

An influx of cellular particles was found in the dermal areas of infected sites in experimentally infected calves with *T. verrucosum* starting on day 5 following infection and increasing until day 33. Immune cells detected in the cellular response were macrophages, $CD4^+$ and γδ T lymphocytes, and a minimum amount of $CD8^+$ lymphocytes. Maximum cellular response were reported by day 33, including γδ T and $CD8^+$ lymphocytes [18]. In experimentally infected cattle with *T. verrucosum*, high levels of macrophages, lymphocytes ($CD4^+$ and $CD8^+$), and $CD4^+$ T helper cells were detected [1]. During dermatophyte infection, cellular immune responses mainly occur in the dermis while the dermatophyte is on the epidermis. In dermatophyte-infected areas of calves infected with *T. verrucosum*, macrophages are usually restricted to the dermis [18].

Ringworm infection in domestic animals is mainly caused by dermatophytes [28]. The protective immunity of bovine dermatophytosis mainly depends on the cellular branches of the immune system [29]. T helper type 2 cells are activated by dermatophytosis in cats and dogs, and the cytokines they produce lead to antibody production and secretion, which leads to chronic disease, while activation of Th1 cells stimulates a cell-mediated response characterized by interferon- γ, and interleukins 12 and 2, which leads to recovery [22]. Th1 CMI is linked to resistance to *C. albicans* infection, and $CD4^+$ T-cells are important for controlling Cryptococcus infections, but both $CD4^+$ and $CD8^+$ T cells are required to clear Cryptococcal infections [1].

4. Challenges of Fungal Infections

The emergence of new fungal infections has become a growing public health challenge [30]. Fungi's inherent capacity to respond to selection for environmental challenges results in a wide range of infection methods. This made it possible for disease emergence and spread to new hosts and environments [31]. Fungal pathogens that cause disease in humans can also cause major problems in animals. It can be associated with a high rate of morbidity and mortality. The importance of fungal diseases to humans and animals has grown in the past few decades. Some fungal species responsible for zoonosis are: *Microsporum canis*, *Trichophyton verrucosum*, and *Histoplasma capsulatum capsulatum*. Many antifungal medications used to treat fungal infections in humans are also used to treat fungal infections in animals. But nowadays there is a report of antifungal resistance [5, 31]. Since fungi are multicellular pathogens, they share many similarities with their host cells, making antifungal drug research difficult [32]. Fungal infections must be diagnosis early and treated more effectively [5].

Development of new antifungal drugs should prioritized, and investment in the research of fungal vaccines should be increased as well [33]. Despite numerous challenges that vaccine development faces, such as a variety of host risk factors and fungal pathogenesis strategies, a pan-fungal vaccine has become acceptable since a single antigen is not used [34]. This protects the host against a variety of fungal diseases. Improving our understanding of the immune system is important for developing a successful antifungal vaccination technique and possible immunological products can be designed [35].

5. Conclusion and Recommendations

Mycosis is a disease caused by fungi. Numerous types of these fungal pathogens are opportunistic, causing ailments in immunosuppressed hosts. The defense mechanisms in the immunocompetent host are effective against fungal pathogens. Fungal infections occur as a consequence of interaction between fungi pathogenicity and host susceptibility. Immunity is an organism's resistance to infection, and adaptive and innate immune systems are defense mechanisms involved in animal immune systems against fungi. The innate immune system is a nonspecific first line of defense against fungal pathogens. Adaptive immunity, on the other hand, is specific and lymphocytes are involved which have a distinct antigen receptor. In the destruction of fungal particles, the cell-mediated immune reaction is critical. However, currently there is no effective vaccine and antifungal drug against fungal infections. This makes it difficult to control the disease. Therefore, improve management of animals and treat concurrent infections to strengthen their immunity. In addition, further study on the immune components involved in fungal infections to develop new diagnostics, anti-fungal drugs and vaccines are recommended.

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