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Immune response to fungal infections

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Abstract

The immune mechanisms of defence against fungal infections are numerous, and range from protective mechanisms that were present early in evolution (innate immunity) to sophisticated adaptive mechanisms that are induced specifically during infection and disease (adaptive immunity). The first-line innate mechanism is the presence of physical barriers in the form of skin and mucous membranes, which is complemented by cell membranes, cellular receptors and humoral factors. There has been a debate about the relative contribution of humoral and cellular immunity to host defence against fungal infections. For a long time it was considered that cell-mediated immunity (CMI) was important, but humoral immunity had little or no role. However, it is accepted now that CMI is the main mechanism of defence, but that certain types of antibody response are protective. In general, Th1-type CMI is required for clearance of a fungal infection, while Th2 immunity usually results in susceptibility to infection. Aspergillosis, which is a disease caused by the fungus *Aspergillus*, has been the subject of many studies, including details of the immune response. Attempts to relate aspergillosis to some form of immunosuppression in animals, as is the case with humans, have not been successful to date. The defence against *Aspergillus* is based on recognition of the pathogen, a rapidly deployed and highly effective innate effector phase, and a delayed but robust adaptive effector phase. *Candida albicans*, part of the normal microbial flora associated with mucous surfaces, can be present as congenital candidiasis or as acquired defects of cell-mediated immunity. Resistance to this yeast is associated with Th1 CMI, whereas Th2 immunity is associated with susceptibility to systemic infection. Dermatophytes produce skin alterations in humans and other animals, and the essential role of the CMI response is to destroy the fungi and produce an immunoprotective status against re-infection. The resolution of the disease is associated with a delayed hypersensitive response. There are many effective veterinary vaccines against dermatophytoses. *Malassezia pachydermatis* is an opportunistic yeast that needs predisposing factors to cause disease, often related to an atopic status in the animal. Two species can be differentiated within the genus *Cryptococcus* with immunologic consequences: *C. neoformans* infects predominantly immunocompromised hosts, and *C. gattii* infects non-immunocompromised hosts. *Pneumocystis* is a fungus that infects only immunosupressed individuals, inducing a host defence mechanism similar to that induced by other fungal pathogens, such as *Aspergillus*.

Keywords: Immunity; Aspergillus; Candida; Dermatophyte; Cryptococcus; Pneumocystis; Malassezia; Pathogenicity

1. Mycoses

Mycoses, conditions in which fungi pass the resistance barriers of animals and establish infections, are a group of diseases with very varied clinical manifestations. Mycoses are of growing importance for the following reasons (Garcia and Blanco, 2000):

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(1) They are produced by fungi that are widely distributed in the environment and, therefore, very difficult to eradicate.
(2) The clinical manifestation of disease caused by fungal infection can be highly variable. For example, in the case of aspergillosis, with effects on very diverse organs, there is a variety of responses, such as local (aspergilloma), systemic (renal, lung, nervous central system, etc.) or even allergic (allergic bronchopulmonary aspergillosis in human).
(3) Diagnosis of these diseases can be problematic because of the difficulty of interpreting the very different clinical pictures in individuals in the presence of colonization, infection and/or disease.
(4) There is a few varieties of vaccines available against these diseases, which are therefore difficult to prevent. At this time, vaccines are limited to a few animal species, to only a few processes and with variable effectiveness.
(5) Treatment is problematic: compared to the antibacterials, the number of antifungal drugs available at present is very small, with much greater difficulty in production, with many side-effects, and with the possibility of the appearance of resistance, as has happened with antibiotics in the treatment of bacterial infection.

In human medicine, the appearance of AIDS and the evolution of immunosuppressive treatments essential for the success of organ transplants, have highlighted the importance of fungal diseases, and efforts have been made to understand these diseases and to develop means for their prevention and control. This evolution has been much slower in veterinary medicine; on many occasions the fungal diseases have been relegated to post-mortem discoveries.

At present, the two main foci of attention in the study of fungal diseases are as follows:

(1) The mechanisms of pathogenicity that cause usually saprophytic fungal species to transform into an aggressor toward an animal host causing disease or even death.
(2) Mechanisms of the host resistance to infection and disease.

In this review, we discuss this second point in detail in an attempt to identify the main mechanisms used by the host immune system to counter fungal infection. A disease outcome is simply a result of the clash between the mechanisms of pathogenicity of the fungi and the mechanisms of resistance of the host, leading to the removal of the infection or its progression according to the imbalance of these mechanisms.

At present, much of what is known about fungal infections is limited to what happens in man. There are many preliminary results obtained with laboratory animals, mainly with murine models. Less is known in the case of domestic animals concerning fungal diseases, especially by species that produce disseminated processes. These are considered to be characteristic of immunocompromised individuals in humans, while in many cases this immunosuppression is not detected in animals. The question is raised of whether immunosuppression exists or have we not been able to detect it.

2. Immune response to fungi: innate and adaptive immunity

Host defence mechanisms against fungi are numerous, and range from protective mechanisms that were present early in the evolution of multicellular organisms (innate immunity) to sophisticated adaptive mechanisms that are induced specifically during infection and disease (adaptive immunity) (Romani, 2004).

Traditionally, innate immunity has been considered as simply a first line of defence. Nevertheless, innate immunity has recently received attention because, despite a certain lack of specificity, it effectively distinguishes self from non-self and activates adaptive immune mechanisms by the provision of specific signals (Medzhitov and Janeway, 1997; Romani, 2004). The innate immune system confers rapid recognition of microbial infection through a limited repertoire of germ line-encoded receptors that recognize a group of conserved molecular patterns common to broad groups of microbial species (Janeway and Medzhitov, 2002; Roeder et al., 2004).

The first of the defensive innate mechanisms is the physical barriers that separate the organism from the environment: i.e. skin and the mucous membranes of the respiratory, gastrointestinal and genito-urinary tracts. The skin and mucous membranes are physical barriers, and they have antimicrobial substances on their surface, some of them synthesized by the epithelial and endothelial cells. Also, they have a commensal microflora of saprophytic microorganisms that impede colonization by pathogenic microorganisms (Romani, 2004).

Once the fungi have passed the physical barriers, they are met with a series of innate mechanisms of defence, including cellular membranes, cellular recep-