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Review

Usefulness of the murine model to study the immune response against *Histoplasma capsulatum* infection

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ABSTRACT

The present paper is an overview of the primary events that are associated with the histoplasmosis immune response in the murine model. Valuable data that have been recorded in the scientific literature have contributed to an improved understanding of the clinical course of this systemic mycosis, which is caused by the dimorphic fungus *Histoplasma capsulatum*. Data must be analyzed carefully, given that misinterpretation could be generated because most of the available information is based on experimental host–parasite interactions that used inappropriate proceedings, *i.e.*, the non-natural route of infection with the parasitic and virulent fungal yeast-phase, which is not the usual infective phase of the etiological agent of this mycosis.

Thus, due to their versatility, complexity, and similarities with humans, several murine models have played a fundamental role in exploring the host–parasite interaction during *H. capsulatum* infection.

Contents

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1. Introduction

Histoplasmosis, which is caused by the dimorphic fungus *Histoplasma capsulatum*, is considered a common systemic mycosis worldwide with well-known endemic geographic areas in many countries, predominantly in the Americas. The disease primarily affects the host mononuclear phagocyte system, and its severity and clinical forms depend on the host's immunological conditions, the infective inoculum size, and the virulence of the involved fungal isolate. In most patients, the infection is self-limited and produces only residual calcifications in the lungs and, sometimes, in the spleen [1,2]. The severe course of histoplasmosis is often associated with its epidemic form. Fungal virulence and exposure to a high concentration of infective propagules, which are primarily present in enclosed spaces that contain bat and bird droppings that foster fungal growth, contribute to the severe outcome of the disease in either immunocompromised or immunocompetent hosts [3–5]. The infection is acquired by the inhalation of airborne infective propagules, mainly microconidia and hyphal fragments, which are produced by the mycelial morphotype (M-phase) of the fungus. The main target organ in the infected host is the lung and, usually, once the infective propagules reach the alveoli they are phagocytosed by alveolar macrophages. Within macrophages, the infective propagules begin their dimorphic transition to the yeast morphotype (Y-phase), which is the parasitic and virulent *H. capsulatum* morphotype [6,7].

Histoplasmosis has been reported in different wild and captive mammals [8–15]; moreover, different mammalian species have been tested in the laboratory as models for experimental histoplasmosis [16–18]. Undoubtedly, mice are the most frequently used animal model to study either histoplasmosis characteristics, such as etiopathogenesis, immunology, diagnosis, and therapy, or fungal characteristics, such as phenotypic variations and genetic diversities. The ability to control numerous characteristics of the animal model allows researchers to mimic the human disease status and to monitor the course of the disease. However, any single experimental model cannot always answer all questions regarding host–parasite interactions because different animal species or distinct routes of infection can produce unexpected results.

To follow the course of experimental histoplasmosis infection different animal species and methodological procedures, involving lung exposure to *H. capsulatum* yeasts, are used. These conditions have distinct strengths and weaknesses concerning fungal infection modeling and the host immune response. There is great variability in animal's susceptibility to fungal infection, which depends on the animal species [19–21]. Sometimes, susceptibility change in the same animal species depends on the animal strain used, as occurs in the murine model, which could interfere in the outcome of experimental histoplasmosis [22,23]. Host susceptibility also depends on the route of infection (inhalation, involuntary instillation, intra-tracheal, intraperitoneal, and intravenous), the inoculum size, the pathogen's virulence, the discriminated expression of their surface molecules that act as pathogen-associated molecular patterns (PAMPs), and the methodologies that are involved in the selected search.

Human cell-lines, murine cell-lines, and *in vitro* differentiated mammalian-cells have been extensively used as models to study host-*H. capsulatum* interactions. Additionally, *in vivo* models, such as invertebrates (the nematode – *Caenorhabditis elegans* and the insect – *Galleria mellonella*) [24–26] and the protozoa – *Acanthamoeba castellanii* [27], have been employed to explore these interactions. However, the aforementioned models have a critical limitation because they do not develop the complexity of the entire mammalian immune defense.

In the absence of an ideal model, it is more suitable to use mice due to their similarity to the human immune system performance. Based on the aforementioned antecedents, the aims of the present review were: to underline the immunological events that are most frequently detected in mice coursing with *H. capsulatum* infection; and to contribute to a better understanding of the plasticity of the host response in experimental conditions.

2. Queries regarding the murine histoplasmosis model

Several mouse strains have been assessed as experimental models in histoplasmosis, particularly BALB/c, C57BL/6, AKR/J, A/J, and Swiss mice [7,22,23,28–34]. In addition, some mouse strains have been classified as susceptible or resistant to the disease, although this categorization is arbitrary and varies depending on the goal of the study [22,23].

Generally, two atypical conditions have been favored in the laboratory to establish murine systemic histoplasmosis: the use of the parasitic and virulent Y-phase (non-infective) as the inoculum and the handling of intraperitoneal or intravenous infection routes (non-natural routes). In contrast, the natural infection route of histoplasmosis, which is through the inhalation of aerosolized *H. capsulatum* M-phase infective propagules, has been scarcely employed in experimental circumstances [23]. Therefore, results of experimental infections must be analyzed cautiously to avoid incorrect conclusions.

3. Dimorphic transition is required for *H. capsulatum* pathogenic mechanisms

The first line of the host defense against *H. capsulatum* obviously involves the mucosa of the upper and lower

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