Role of Complement in Fungal Infections

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1. Introduction

The complement system is a component of host resistance where innate and adaptive immunity intersect. Innate resistance is invoked when a microbe activates the alternative pathway or when mannan-binding lectin binds to a microbe and activates the classical pathway. The adaptive immune system utilizes the complement system when an IgG or IgM antibody binds to a microbial surface and activates the classical pathway.

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Regardless of the manner of activation, the consequences of activation of the complement system include deposition of opsonic serum proteins on a microbial surface that facilitate phagocytosis by macrophages and neutrophils, attraction of inflammatory cells to the site of infection through the release of chemotactic peptides, and activation of a cascade of proteins that comprise the membrane attack complex that may produce damage to membranes on the surface of cells on which complement activation occurs. Fungi are surrounded by thick carbohydrate cell walls, which likely restrict complement-mediated killing, but opsonization and promotion of an inflammatory response are critical components of host resistance to fungal infection.

Fungi have served as model targets for the study of complement activation for over 100 years. von Dungern reported in 1900 that treatment of serum with yeast cells inactivates a heat-sensitive component of serum that is normally destructive to bacteria (von Dungern, 1900). This report was confirmed in 1902 in a study by Ehrlich and Sachs (1902). Zymosan, a cell wall product of Saccharomyces cerevisiae, which is rich in glucan content, has been a prototype for study of the alternative complement pathway and mechanisms of opsonization (Pillemer and Ecker, 1941; Fizpatrick and DiCarlo, 1964). Indeed, zymosan led to the discovery of the alternative pathway (Pillemer et al., 1954). Studies of complement activation by pathogenic fungi have built on this legacy of prior work.

Production of many disseminated fungal infections requires that the fungus, usually a yeast cell, spend a portion of its time in the bloodstream. Since serum is rich in proteins of the complement cascade, there is a high probability that the consequences of interaction between a yeast cell and the complement system will have a major impact on the course of disease. This chapter focuses primarily on complement activation by Cryptococcus neoformans and Candida albicans, two fungi that rely on hematogenous dissemination for spread from sites of initial infection to target organs.

2. Activation of the Complement System by Pathogenic Fungi

2.1. Experimental Systems for Study of Complement Activation

Several experimental approaches have been used to study complement activation by pathogenic fungi. In the first approach, microbes are incubated in serum and the biological consequences of complement activation are assessed. As discussed in a later section, the two most commonly studied biological consequences of complement activation are opsonization and release of inflammatory mediators. The second approach is measurement of the depletion of complement proteins as a consequence of complement activation. The standard complement fixation assay is an example of a complement depletion assay. The third approach is immunochemical evaluation of the release of cleavage products of complement proteins via complement activation. Typically, supernatant fluids are examined for fragments of C3 or factor B following incubation of fungi in serum. Finally, complement activation can be assessed by measurement of the deposition of cleavage fragments of C3 onto the fungal surface. Two methods for measurement of C3 deposition are: use of radiolabeled C3 and immunofluorescence. Radiolabeled C3 is advantageous because it allows for a quantitative assessment of C3 binding. Staining for C3 binding by immunofluorescence is valuable because it identifies the sites of C3 binding. Given the critical role of C3 fragments in opsonization, both quantitative and qualitative examination of C3 binding