CHAPTER 14

PNEUMOCYSTIS

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Abstract: Pneumocystis is an opportunistic fungal pathogen most prevalent in HIV+ individuals. Despite a significant reduction in the incidence of Pneumocystis pneumonia following the advent of highly active anti-retroviral therapy (HAART), Pneumocystis remains the number one AIDS-defining illness. The host response to Pneumocystis involves a fine balance between cellular activation leading to organism clearance and lung injury associated with the immune response. This review will focus on the innate and adaptive cellular immune responses to Pneumocystis infection, specifically, immune recognition, clearance of infection and resolution of inflammation will be discussed.

Keywords: Pneumocystis, immunosuppression, pulmonary immunity

1. INTRODUCTION

Pneumocystis carinii organisms were originally described as part of the trypanosomal life cycle and thought to be protozoans for many decades. Sequencing of the small subunit ribosomal RNAs from rat Pneumocystis (Edman, Kovacs et al. 1988) and subsequent total RNA sequencing (Stringer, Stringer et al. 1989) determined the organism was a fungal pathogen rather than a protozoan as originally thought. Pneumocystis is an atypical fungal pathogen with high levels of cholesterol present in the cell membrane rather than the fungal sterol, ergosterol (Kaneshiro, Ellis et al. 1994). The trophozoite form of the organism, characterized as 3–6 μm in diameter, is the predominant form present in the lung; the cyst form is slightly larger, 4–8 μm in diameter, and contains numerous cysts. Pneumocystis organisms isolated from different host species exhibit genetic heterogeneity despite being morphologically similar (Wakefield 1998). As a result of this genetic heterogeneity a nomenclature system has been established such that the host can be identified. Under this system mouse-derived Pneumocystis is known as P. carinii sp. f. muris

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and human-derived is *P. carinii sp. f. hominis* with each organism designated a special form based on the host it is derived from (Redhead, Cushion et al. 2006). Genetic variation coupled with the inability to grow the organism in vitro make studying *Pneumocystis* pneumonia (PCP) especially difficult.

The earliest reported cases of PCP occurred in malnourished children from European orphanages during World War II. Immunocompromised patients were also found to be at risk for developing PCP. A substantial increase in the number of PCP cases was seen following the beginning of the AIDS epidemic of the early 1980s. Peripheral CD4+ T-cell levels below 200 cells/µl were found to be the primary risk factor for HIV+ patients to develop PCP (Phair, Munoz et al. 1990; Stansell, Osmond et al. 1997). The introduction of anti-*Pneumocystis* prophylaxis in 1989 and highly active antiretroviral therapy (HAART) in 1996 has led to a significant decrease in the incidence of PCP. Despite the decline in opportunistic infections associated with HIV PCP remains the most common AIDS-defining illness in the United States (Kaplan, Hanson et al. 2000; Morris, Lundgren et al. 2004). These studies found patients not receiving medical care, or non-adherent to treatment, possible drug-resistance and decreased efficacy of treatment when CD4+ T cell counts are low contribute to the inability to eradicate PCP in susceptible populations.

The mode of transmission of *Pneumocystis* has yet to be determined with certainty. Reactivation of latent infection when a patient becomes immunocompromised is the traditional theory of infection supported by studies showing the majority of healthy children test positive for anti-*Pneumocystis* antibodies by the age of 4 years (Pifer, Hughes et al. 1978; Peglow, Smulian et al. 1990; Morris, Beard et al. 2002). Alternatively, clusters of PCP outbreaks suggest airborne person-to-person transmission is likely (Morris, Beard et al. 2002). *Pneumocystis* appears to be ubiquitous in nature and its’ DNA sequences have been identified in samples of air spora and soil (Wakefield 1996). One study of HIV+ patients found gardening or camping to increase the risk of developing PCP (Navin, Rimland et al. 2000). While a definitive answer regarding the transmission of *Pneumocystis* has not been reached it is clear that patients with weakened immune systems are especially at risk for developing pneumonia and investigation into the host defense against *Pneumocystis* is of critical importance.

This chapter will focus on the innate and adaptive immune response against *Pneumocystis* infection. A successful host response against a pathogen involves receptor-mediated recognition, activation of the innate and adaptive immune systems to release inflammatory mediators and oxidants, but also resolution to prevent excessive organ injury. The role of alveolar macrophages, thought to be the key effector cells against *Pneumocystis*, will be reviewed in detail. With regard to adaptive immunity the requirement for CD4+ T cells to prevent infection will be discussed, as will the controversial role of CD8+ T cells. Elucidating the cellular responses involved in PCP-related pathology and clearance of infection remain of central importance as the decline in the rate of infection has leveled off and PCP remains a prevalent opportunistic infection.