PNEUMOCYSTIS: AIDS RELATED MYCOSIS; WHAT ARE THE HOST INNATE IMMUNE MECHANISMS CONTROLLING INFECTION?

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Background

There is a high prevalence of infectious diseases such as HIV/AIDS on the African continent which render patients immunocompromised. Strongly associated with this is the prevalence of life-threatening opportunistic fungal infections. With 1.5 million deaths annually, fungi kill more people than Malaria and almost as many as Tuberculosis. Despite this, fungal infections are an overlooked clinical and public health issue. *Pneumocystis jirovecii,* causes pneumonia (PCP) in HIV/AIDS patients, with an estimated 400,000 cases and 150,000 deaths per annum. Although the use of highly active antiretroviral therapy has decreased the incidence of PCP, the morbidity and mortality remain high. In Sub-Saharan Africa (SSA), data is limited due to clinical and diagnostic challenges. Furthermore, the impact of how other pathogens commonly found in SSA like *Mycobacterium tuberculosis* (MTB) and helminths affect the prevalence of PCP is yet to be demonstrated. Innate immunity driven by pathogen recognition has important downstream effects on adaptive responses. Both Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) have been identified as important pattern recognition receptors (PRR) and are critically involved in cytokine responses to fungi. Increasing evidence highlights an important role for the synergistic signaling of both TLRs and CLRs in fungal recognition and antifungal immunity. Furthermore, restoration of missing signaling pathways for example by using exogenous toll-agonists, have been proven to be crucial in pathogen clearance as seen in chromoblastomycosis. Our study thus aims to identify the host innate immune mechanisms responsible for controlling *Pneumocystis* infection.

Methods

By using a Pneumocystis mouse model and mice deficient in CLRs including Dectin-1, Clecsf8 (Cle4d, Mcl, Dectin 3) or the downstream signalling molecule Pkcδ (protein kinase c delta), we hope to dissect the innate immune response in *Pneumocystis murina* (PcM) infection. Briefly, Dectin-1, Clecsf8/MCL, Pkcδ deficient mice will be infected with (PcM) cysts and disease progression determined at 1, 2, and 3 weeks post infection .Furthermore, using the immunocompromised RAG-$1^{-/-}$ mice we will investigate the potential influence of Helminth infection on *Pneumocystis* clearance. Briefly, $Rag1^{-/-}$ mice will be infected with *Nippostrongylus brasiliensis*. One week post infection, mice will be infected with PcM and disease progression determined at 2 weeks post PcM infection.

Results

Preliminary data using Pkcδ-/- mice that has been shown to engage Syk Kinase-coupled C-type lectin receptors, shows significant higher lung burden compared to the wild type mice suggesting Pkcδ plays a role in the immunity against *Pneumocystis* infection**.** Furthermore, co-infection with Helminths promote PcM clearance.

Conclusion

With the indicative preliminary results, and continual investigation, we hope to discover new insights into underlying host mechanisms involved in protective immunity to *Pneumocystis* which may lead to improved treatments for immunocompromised hosts. Furthermore, the mechanism of enhanced fungal recognition and clearance driven by existing infections could explain the lower prevalence of PCP in Sub-Saharan Africa.