My Guests: Dr. Karen Wozniak and Fungal Infections

Dr. Karen Wozniak received her doctorate in the fields of immunology and parasitology at the institution of Louisiana State University; studying and orientating herself through years of rigorous study, she has now become a specialist in the human microbiota (a human’s personal microbes) and immunity: innate and adaptive. Now a member of the microbiology department at Oklahoma State University, she has constructed a lab that is interested in studying the role of innate immune cells in protection against fungal infections, particularly their role in protection against the opportunistic fungal pathogen *Cryptococcus neoformans*, which is the leading cause of fungal meningitis. Fungal microbes can infect humans. Thus, her and her teams current research focuses understanding the interaction between *C. neoformans* and dendritic cells (DCs) - antigen-presenting cells of the immune system. They act as messengers between the innate and the adaptive immune systems - and macrophages (“big eaters” that are large cells that eat any bacteria and virus-infected cells they encounter) and understanding their role in the initial control of this infection.

Current Work: There are three main projects in her lab: 1) examining the mechanism involved in fungal cell wall degradation (destruction) by the lysosomal enzyme cathepsin B, 2) examining dendritic cell (DC) factors associated with killing the fungal pathogen *Cryptococcus neoformans* and 3) determining mechanisms that are responsible for macrophage killing versus intracellular growth of fungal pathogens (agents that cause disease). *Cryptococcus neoformans* is an opportunistic fungal pathogen that primarily affects immune compromised patients. The disease begins as a pulmonary infection that eventually spreads to the central nervous system causing meningitis. Current estimates suggest that approximately 275,000 people are infected with this pathogen each year, and approximately 180,000 die each year due to cryptococcal meningitis (Rajasingham et al, The Lancet, 2017). The initial interaction with the host begins in the lung, and the innate immune cells of the lung (primarily macrophages and dendritic cells) are the front-line of defense against this pathogen from hurting us.

**Mechanism by which the lysosomal (organelle that degrades peptidoglycan, which is the outer membrane in gram-negative bacteria) enzyme cathepsin B (lysosomal cysteine protease) degrades the cryptococcal cell wall**: Her project will examine mechanisms involved with cathepsin B degradation of the cryptococcal cell wall. They have shown that the lysosomal enzyme, cathepsin B, can kill *C. neoformans*. This occurs because of the formation of a hole in the cell wall and leads to osmotic lysis (breaking) of the organism (Hole et. al, Scientific Reports, 2012). However, the mechanism of activity of cathepsin B on the fungal cell wall components has yet to be fully understood.

**DC lysosome factors associated with killing *C. neoformans***: This project will identify components present in the lysosome of dendritic cells (DCs) that are responsible for killing of the organism. Many other anti-fungal components exist in the lysosome, and they have divided the lysosomal extract and have shown that several pieces have anti-cryptococcal activity. Currently, the team is performing studies to identify these components. Following identification, these components will be used to determine both the components responsible for anti-fungal activity as well as the mechanisms by which can kill the fungus.

**Mechanisms governing fungal intracellular (inside) growth vs intracellular (outside) killing in macrophages**: This project examines the macrophage side of the interaction of fungal pathogens, including *C. neoformans*, with different forms of macrophages. Many laboratories have examined intracellular (inside) growth of *C. neoformans* and other fungal pathogens inside of macrophages. Dr. Wozniak have shown that the interaction of *C. neofomans* with two different types of human macrophages results in two different outcomes – intracellular growth or intracellular killing. She and her team are currently planning to perform RNA sequencing in order to determine different gene expression in each type of macrophage upon interaction with the fungal disease.

These current studies can also be applied to other fungal pathogens. The ultimate objective of these studies is to identify ways used by anti-fungal macrophages that could be applied as immunotherapy against fatal *C. neoformans* infections. Humans and infectious microbes have been combating since prehistoric times. Why is any of this relevant? Well, fungi are generally harder to treat than bacteria due to fungi being eukaryotes which makes them more similar to our own cells; it is harder to find potent microfungals that are not harmful to us. Moreover, fungi have a drug detoxification system that can turn off many antimicrobial agents. While not typically mentioned in the same category as cancer or HIV, fungal infections can be just as severe. With every new implementation of antibiotics or proactive measures to deter infections, microbes continue to fight back; but if we have individuals whom possess the same cerebral and creative scientific merit as Dr. Wozniak, then the world (excluding pathogens) is in safe hands.

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Rajasingham, R., Smith, R. M., Park, B. J., Jarvis, J. N., Govender, N. P., Chiller, T. M., ... & Boulware, D. R. (2017). Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *The Lancet infectious diseases*, *17*(8), 873-881.

Wozniak, K. (2019, April 9th). Personal interview.