**IMMUNE RESPONSE INVESTIGATION**

INTRODUCTION

The immune system encompasses many cells, tissues and organs working together to keep us healthy every day. A fond researcher of the Immune system and the fungus *Cryptococcus neoformans*, Dr. Karen Wozniak, provided our paper with an in-depth discussion on a recent study with her colleagues on innate immune cells developing memory against this fungus. Dr. Wozniak of Oklahoma State University’s Microbiology and Molecular Genetics received her Doctor of Philosophy in Immunology and Parasitology from Louisiana State University Health Science Center in 2004. Her current lab interests at OSU are studying the mechanisms by which C. neoformans interact with dendritic cells and macrophages and their role in opportunistic infection. Dr. Wozniak and her colleagues were involved in investigating the priming of macrophages which resulted in an induced innate memory for up to approximately 70 days (1).

The response to pathogens that attack the human body daily are met by two responses in the human body. The first is the innate response comprised of your skin as a barrier, commensal organisms that compete with foreign invaders for space on your skin, and eventually the first immune cells respond if infected (1). The primary cells responsible are macrophages, natural killer cells, dendritic cells and neutrophils; the adaptive immune responders are comprised of dendritic cells, B cells and T cells (1). Adaptive responses are memorized by memory B cells and T cells over time to provide protection for subsequent infections (1). Interestingly, the innate immune response is not typically known to have immunological memory for subsequent infections. The recent concept of the “trained innate immune” system has been observed in plants, insects, and mammals. This is a vital area of research because many individuals with a weakened immune system lack a strong adaptive immune response that typical vaccination strategies target to induce immunological memory (1).

STUDY RESULTS

Dr. Wozniak’s primary investigation with her colleagues was elucidating how mice were able to retain memory of a primary challenge of IFN-γ-producing (a pro-inflammatory signaling molecule) strain of *C. neoformans* and fight off a subsequent infection of the same pathogen. Initially the authors sought to determine the effector cell responsible for this memory, so the investigators used mice deficient of both adaptive B and T immune cells. Interestingly, mice with no B, or T cells, neutrophils or natural killer cells, were still protected in 100% of the mice after the subsequent infection (1). On top of the memory developed by the macrophages, the response was more specific to *C. neoformans* and was determined to not provide sufficient memory for other tested pathogens such as *Candida albicans*, and *Staphylococcus aureus* (1).

This response by the macrophages introduced a question on how macrophages utilize epigenetics (alterations in gene expression) in this response. The investigators utilized a software application at core facility using Ingenuity Pathway Analysis (IPA) that elucidated the mechanism by which memory is developed via whole transcriptome analysis, which is the entirety of mRNA products made by the cell analyzed by the software. This analysis indicated the STAT1 pathway and other pathogen response pathways are activate in the macrophages (1). Beyond the gene expression pathways discovered to be active after the primary response, the investigators found that specific methylation patters on histones of the DNA were responsible for the epigenetic modifications utilized in subsequent infection (1).

DISCUSSION

These results contribute to the concept of the “trained innate immunity” that is a developing field for alternative strategies in advancing human health. Dr. Wozniak and her colleagues were able to determine the mechanism by which macrophages primed by introducing IFN-γ producing strain of *C. neoformans*. This stimulation alters the macrophage into the M1 phenotype which has pro-inflammatory response to protect against non-IFN- γ producing *C. neoformans* for up to 70 days in the murine models (1).

REFERENCES

Leopold Wager, C. M., Hole, C. R., Campuzano, A., Castro-Lopez, N., Cai, H., Caballero Van Dyke, M. C., … Wormley, F. L. (2018). IFN-γ immune priming of macrophages in vivo induces prolonged STAT1 binding and protection against Cryptococcus neoformans. PLOS Pathogens, 14(10). https://doi.org/10.1371/journal.ppat.1 007358