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DISSERTATION

"Infiltrating monocytes promote host survival by preventing helminth-induced brain inflammation"

by

Chandler Sy

M.D./Ph.D. Program

B.S. 2013, The College of New Jersey, Ewing, NJ

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Wednesday, April 3rd, 2019
10:30 A.M.
Cancer Center G1196

ABSTRACT

Helminth parasites represent an enormous public health concern and are amongst the most abundant of all chronic human infections. Protective responses to helminths are associated with the production of type 2 cytokines, the development of CD4+ T helper type 2 (T_H2) cells and the induction of alternatively activated (M2) macrophages. Recent studies have found that M2 macrophages play critical roles in promoting both worm expulsion and the healing of helminth-affected tissues. Despite these advances, whether protective M2 responses are initiated by tissue-resident or monocyte-derived macrophages remains poorly understood. Here, we show that mice depleted of bone marrow-derived monocytes exhibit dramatic weight loss and increased mortality following *Trichinella spiralis* infection. Immunologic and pathologic analyses revealed that increased morbidity and mortality following *T. spiralis* infection was occurring independently of parasite burdens, intestinal barrier defects, alterations in liver or kidney, or appetite suppression. However, RNA-seq analysis of brain tissue revealed that mice depleted of C-C motif chemokine receptor 2 $(CCR2)^+$ monocytes exhibited infection-induced proinflammatory signatures characterized by the increased expression of tumor necrosis factor (*Tnf*), *il1b*, *Il6*, *Il12b*, and NLR family pyrin domain containing 3 (*Nlrp3*). In support of this finding, microglia from mice depleted of $CCR2^+$ monocytes exhibited a more activated morphology and expressed higher levels of infection-induced proinflammatory cytokines compared to controls. Importantly, flow cytometric analysis and single-cell RNA sequencing studies revealed that $CCR2^+$ monocytes and their derived cell populations are increased in the brain following infection and express genes associated with regulating inflammation. These data suggest that $CCR2^+$ bone marrow-derived monocytes perform essential host-protective responses and regulate inflammatory cytokine production in the central nervous system (CNS) following *T. spiralis* infection.