Neuroscience Graduate Program

presents:

PATRICK MILLER-RHODES

ADVISOR:

HARRIS GELBARD

IN A THESIS PROPOSAL

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10:00AM IN AUDITORIUM K-307 (3-6408)

Diametric control of microglial phenotype by Mafb and PU.1 during HIV-1 infection

The advent of combination antiretroviral therapy (cART) has largely eliminated the incidence of encephalitis-like inflammation in human immunodeficiency virus-1 (HIV-1) patients; however, HIV-1-associated neurocognitive disorder (HAND) persists in virologically suppressed patients. HAND is observed in ≥50% of HIV-1-infected individuals in countries with widespread access to cART [1]. Recent neuropathological findings indicate that neuroinflammation exists in the absence of encephalitis and productive viral replication in the CNS of HIV-1 patients [2]. Concurrently, next-generation sequencing technologies have vastly expanded our knowledge of factors that regulate microglial development and homeostasis [4,5,6], permitting an examination of their relevance to disease processes. Among these are the master regulator transcription factors Mafb and PU.1, which have been shown to specify molecular signatures corresponding to homeostatic [6] and activated microglial phenotypes [7,8], respectively. The primary goal of this thesis proposal is to identify the contributions of Mafb and PU.1 to microglial homeostasis and microgliosis, respectively, in the context of chronic HIV-1 infection. To this end, I propose three aims. First, I will determine whether microglial PU.1 expression is positively correlated with microgliosis, defined using proliferation markers and morphological analysis of microglia in brain sections isolated from HIV-1 infected humanized NOD/SCID/IL2Rγc-/- (hNSG) mice. Second, I will use a CRISPR/Cas9-based activation approach to over-express Mafb and PU.1 from their endogenous loci in human microglia. I will use a combination of RNA-seq, Gene Ontology analysis, and chromatin immunoprecipitation experiments to determine whether high Mafb and PU.1 expression contribute to microglial pro-inflammatory output and proliferation. Third, I will determine whether the mixed lineage kinase 3 inhibitor URMC-099 promotes Mafb expression in cultured human microglia and in CNS-resident phagocytes in HIV-1-infected hNSG mice. Altogether, the proposed experiments will identify key roles for Mafb and PU.1 in defining features of microglial physiology in the context of chronic HIV-1 infection.