M & I
Microbiology
and Immunology
University of North Carolina at Chapel Hill

DISSERTATION SEMINAR

Jason Wong

"Role of Kinases in Kaposi's Sarcoma-Associated Herpesvirus Pathogenesis."

Friday, November 15, 2019
1:30 p.m.
Joseph S. Pagano Conference Room (00-002)
Lineberger Comprehensive Cancer Center

Dissertation Advisor: Dr. Blossom Damania

Presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy

ABSTRACT

Jason Wong: Role of Kinases in Kaposi's Sarcoma-Associated Herpesvirus Pathogenesis
(Under the direction of Blossom Damania)

Kaposi's sarcoma-associated herpesvirus (KSHV) is associated with four diseases: Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), multicentric Castleman's disease (MCD), and KSHV-associated inflammatory cytokine syndrome (KICS). KS is the most common AIDS defining malignancy, and even though long term remission is possible, KS often relapses and there is no evidence that suggests KS can be cured. PEL is a B-cell non-Hodgkin lymphoma (NHL) that has a poor prognosis with a median survival time of about six months. Therefore, there is a need to develop alternative therapies for KSHV-associated malignancies. KSHV modulates several cellular signal transduction pathways, some of which play a role in tumorigenesis. Kinases often control the propagation and signaling within these pathways. In this dissertation we examine how both host (Chapter 2) and viral kinases (Chapter 3) modulate KSHV pathogenesis, which may lead to the development of targeted therapies to treat KSHV-associated diseases. Characterization of host kinases which have upregulated activity in PEL in comparison to healthy B-cells and other B-cell NHLs led to the discovery that the receptor tyrosine kinase, Tyro3 is uniquely upregulated in PEL. Tyro3 drove survival in PEL cells by upregulating the phosphoinositide-3-kinase (PI3K) pathway. We developed an inhibitor against Tyro3, which inhibited growth and PI3K signaling in PEL cells, and resulted in a decrease in tumor burden in a PEL xenograft mice model. We also characterized a viral kinase encoded by KSHV known as viral protein kinase (vPK). Since previous work in our lab has shown vPK upregulates protein synthesis and overexpression of vPK in mice results in an increased rate of developing lymphomas, we were interested in characterizing possible host protein interactors of vPK that may play a role in KSHV pathogenesis. We found that vPK binds the tumor suppressor, protein phosphatase 6 (PPP6). We also characterized vPK's effect on mitophagy, a selective form of autophagy that targets mitochondria for degradation.