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

DISSERTATION SEMINAR

Carolina Caro-Vegas

"Pathogenesis and Treatment of Kaposi's Sarcoma-Associated Herpesvirus Related Diseases."

Tuesday, April 16, 2019
2:00 p.m.
Joseph S. Pagano Conference Room (00-002)
Lineberger Comprehensive Cancer Center

Dissertation Advisor: Dr. Dirk Dittmer

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

ABSTRACT

Carolina Caro-Vegas: Pathogenesis and Treatment of Kaposi's Sarcoma-Associated Herpesvirus Related Diseases
(Under the direction of Dirk Dittmer)

Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and KSHV-associated multicentric Castleman disease (KSHV-MCD) and KSHV-associated inflammatory cytokine syndrome (KICS). KICS is a newly described clinical entity associated with lytic reactivation and high-level, systemic replication of KSHV. We characterized the clinical and laboratory features of a KICS patient over-time. Additionally, we compare the KICS patient to Kaposi's sarcoma (KS) (n=11) and non-KS (n=6) cases. The KICS patient presented elevated levels of KSHV and IL-10, as expected. Treatment with tocilizumab effectively reduce his IL-10 level to undetectable. Surprisingly, this patient did not present high levels of IL-6. We successfully sequenced the whole KSHV genome, which showed no differential mutation before KICS was officially diagnosed and after diagnosis. Phylogenetic analysis of the KICS consensus sequences showed that both sequences aligned to the K1 clade and were closely related to BAC16, JSC1 (cell line) and GK1B sequences. Additionally, KSHV-related malignancies have a highly active mTOR pathway, which makes mTOR a potential therapeutic target. Therefore, we sought to test MLN0128, an ATP-competitive inhibitor of mTOR, as treatment for PEL. Our results demonstrated that MLN0128 has a greater effect on inhibiting proliferation than allosteric mTOR inhibitor rapamycin. MLN0128 has ~30 nM IC_{50}values across several PEL cell lines, including PEL that is resistant to conventional chemotherapy. MLN0128 induced apoptosis in PEL, whereas rapamycin only induced G_1arrest. MLN0128 inhibited phosphorylation of mTOR complex 1 and 2 targets, while rapamycin only partially inhibited mTOR complex 1 targets. PEL xenograft mouse models treated with MLN0128 showed reduced effusion volumes in comparison to the vehicle group. Rapamycin resistant (RR) clones with an $IC_{50}$for rapamycin 10 times higher than the parental clones emerged consistently after rapamycin exposure as a result of transcriptional adaptation. MLN0128 was nevertheless capable of inducing apoptosis in these RR clones. Our results suggest that MLN0128 might offer a new approach to the treatment of chemotherapy resistant PEL.