UNC

SCHOOL OF MEDICINE

Microbiology and Immunology

DISSERTATION SEMINAR

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“Interleukin-1 Receptor-Associated Kinase (IRAK) Signaling in Kaposi Sarcoma-Associated Herpesvirus-Induced Primary Effusion Lymphoma.”

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Via Zoom

Dissertation Advisor: Dr. Dirk Dittmer

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ABSTRACT

Jedediah Seltzer: Interleukin-1 Receptor-Associated Kinase (IRAK) Signaling in Kaposi Sarcoma-Associated Herpesvirus-Induced Primary Effusion Lymphoma
(Under the direction of Dirk Dittmer)

Kaposi's sarcoma-associated herpesvirus (KSHV) is necessary but not sufficient for primary effusion lymphoma (PEL) development. Alterations in cellular signaling pathways are also a characteristic of PEL. Other B cell lymphomas have acquired an oncogenic mutation in myeloid differentiation primary response 88 (MYD88). The MYD88 L265P mutant results in the activation of interleukin-1 receptor associated kinase (IRAK). To probe IRAK/MYD88 signaling in PEL, we employed CRISPR/Cas9 technology to generate stable deletion clones in BCBL-1Cas9 and BC- 1Cas9 cells. To look for off-target effects, we determined the complete exome of the BCBL-1Cas9 and BC-1Cas9 cells. Deletion of either MYD88, IRAK4, or IRAK1 abolished interleukin-1 beta (IL-1β) signaling; however, we were able to grow stable subclones from each population. Transcriptome sequencing (RNA-seq) analysis of IRAK4 knockouts (IRAK4 KOs) showed that the IRAK pathway induced cellular signals constitutively, independent of IL-1β stimulation, which was abrogated by deletion of IRAK4. Transient complementation with IRAK1 increased NFκB activity in MYD88 KO, IRAK1 KO, and IRAK4 KO cells even in the absence of IL-1β. IL-10, a hallmark of PEL, was dependent on the IRAK pathway, as IRAK4 knockouts reduced IL-10 levels. We surmise that, unlike B cell receptor (BCR) signaling, MYD88/IRAK signaling is constitutively active in PEL, but that under cell culture conditions, PEL rapidly became independent of this pathway.