

Poster presentation

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The role of the TRAF2/3 binding site in LMP1 and CD40 signaling

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The Epstein-Barr virus encoded protein, LMP1, is a viral mimic of the cellular protein CD40. In comparison to CD40, LMP1 signals to B lymphocytes in an amplified and sustained manner. LMP1 signaling is thought to contribute to the development of lymphoma in patients afflicted with HIV or in transplant recipients who are immunosuppressed. CD40 uses TRAF2 as a positive mediator of its signaling, while TRAF3 serves as a negative regulator. Interestingly, LMP1 uses TRAF3 as a positive mediator of its signaling. CD40, not LMP1, signaling has been shown to degrade TRAF2 and 3. Currently, lack of LMP1-induced TRAF degradation is thought to result in exaggerated LMP1 signals. Because LMP1 binds TRAF2 with less affinity than CD40 and TRAF2 is needed for inducing CD40-mediated TRAF2 and 3 degradation, it was thought that relative affinity for TRAF2 controls the disparate ways in which CD40 and LMP1 use and degrade TRAFs 2 and 3, and that this in turn results from the different sequences of the TRAF2/3 binding sites of the two receptors. However, our recent studies reveal that TRAF binding affinity and TRAF binding site sequence only partially dictates CD40 versus LMP1 signaling properties. We have been studying signaling via hybrid molecules that have had their TRAF binding sites switched so that CD40 contains the TRAF binding site of LMP1 and LMP1 contains the CD40 TRAF binding site. Examination of TRAF binding and degradation, cytokine production, IgM secretion, and the activation of c-Jun kinase and NF-κB revealed that some events are strongly dictated by TRAF binding site sequences, others partially regulated, and still others appear independent of TRAFs 2 and 3.