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Yun Hsuan Lu

Washington University in St. Louis

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RODENT HERPESVIRUS TEXAS (RHVT) ENCODES A HIGH AFFINITY CHEMOKINE DECOY RECEPTOR

Yun Hsuan Lu

Mentor: Daved Fremont

Double-stranded DNA viruses have evolved multiple ways of evading host immune surveillance. Viruses target host cytokines that function as early mediators of host immune response and interfere with cytokine signaling through three mechanisms: viral homologs of cytokines, cytokine receptors, and/or sequence diverse soluble decoy receptors.

M3, encoded by mouse gammaherpesvirus 68 (MHV68), was the first herpesvirus-encoded decoy receptor characterized. M3 broadly recognizes C, CC, CXC, and CX3C chemokines, but exhibits high affinity for certain CC and CXC chemokines. Functionally, M3 inhibits chemokine signaling by binding chemokines through the same determinants as their endogenous receptors, but with a higher affinity. Another chemokine-binding protein from herpesvirus Peru (RHVP) has been identified and characterized. RHVP-encoded R17 shares little sequence similarity with M3, yet is structurally similar to M3 and specifically binds certain CC and C chemokines. R17 also interacts with cell surfaces via cell-surface glycosaminoglycans (GAGs). Functionally, much like M3, R17 antagonizes chemokine signaling.

The sequence of another rhadinovirus, rodent herpesvirus Texas (RHVT), has recently become available. RHVT encodes a protein, T17, that shares 32% sequence similarity with R17. Is T17 also a chemokine-binding protein, and if so, what is its binding specificity? This project focuses on comparing R17 and T17 through a systematic analysis of their GAG and chemokine-binding abilities, and the subsequent effect on chemokine-guided transmigration. Cell staining experiments show that T17, like R17, interacts with GAGs. Direct binding experiments reveal that T17, like R17, recognizes specific CC and C chemokines, but can additionally bind certain CXC chemokines. Functionally, my preliminary data suggest that T17 inhibits CXCL12 and CCL2-mediated transmigration of Jurkat T cells and THP-1 cells, respectively. Having demonstrated that T17 is a chemokine-binding protein, we can now focus on the molecular determinants responsible for its different chemokine-binding specificities, and their effects on the modulation of the host immune system.