Infectious Agents and Cancer

Poster presentation

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Human herpesvirus 8 K1-derived peptides disrupt the inhibitory FAS-K1 complex and restore FAS receptor-mediated apoptosis

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from 11th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI): Basic, Epidemiologic, and Clinical Research
Bethesda, MD, USA. 6–7 October 2008

Published: 17 June 2009

Infectious Agents and Cancer 2009, **4**(Suppl 2):P36 doi:10.1186/1750-9378-4-S2-P36

This abstract is available from: http://www.infectagentscancer.com/content/4/S2/P36

Background

Human herpesvirus 8 (HHV-8) infection is associated with the development of primary effusion lymphoma, Kaposi's sarcoma, and multicentric Castleman's disease. The *K1* gene of HHV-8 is expressed in tumor cells as a transmembrane protein with an immunoglobulin-like domain in its ectodomain and an immunoreceptor tyrosine-based activation motif (ITAM). We demonstrated that K1 protein activates nuclear factor-kappa B (NF-κB), and K1 expression in transgenic mice stimulated accumulation of lymphatic cells and development of lymphoma. How K1 blocks apoptosis and induces hyperplasia and lymphomas is not known. We hypothesized that K1 contributes to lymphoma development partly by suppressing apoptosis, and that this suppression combined with its NF-κB activation produces lymphoma.

Results

We found that K1 binds to Fas and in turn, inhibits Fas-mediated apoptosis. We mapped the region that K1 uses to bind to Fas as an immunoglobulin (Ig) chain-like domain by expressing deletion mutants of K1. Overexpression of an Ig domain-containing protein CD79b competed with K1-Fas binding in a dose-dependent manner. Two 20-amino acid peptides (N251, N253) representing the Ig domain of K1 competed with K1-Fas binding in immunoprecipitation/immunoblotting analysis. The N251 and N253 peptides (100 μM) enhanced anti-Fas antibody (CH-11, 50 ng/mL)-induced apoptosis of BJAB lymphoma cells that expressed K1 but not that of vector-transfected BJAB cells. Ig-deleted K1 (K1dIg)-transfected mice were not protected (0/6), and K1-transfected mice were protected (7/10, $P < 0.01$) against the lethal effects of agonistic anti-Fas (Jo2) antibody. K1dIg expressed in mice did not form complexes with Fas, suggesting that the Ig domain is essential for K1-Fas binding and suppression of apoptosis.

Conclusion

Collectively, these results indicate that K1 potently blocks apoptosis, and that this effect is mediated through the Ig-like domain of K1. Because viral proteins mimic cellular proteins, these results predict the presence of functional cellular homologs of K1 that have key roles in death receptor regulation.