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Poster presentation

Kaposi's sarcoma human herpesvirus K1 interferes with FAS-mediated apoptosis and stimulates clonal growth and lymphoid hyperplasia

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Background

Infection with human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma associated herpesvirus, is associated with the development of primary effusion lymphoma and Kaposi sarcoma. A transmembrane protein of HHV-8, K1, is readily expressed in these tumors, and the expression of K1 alone causes hyperplasia of lymph nodes and lymphomas in mice. The exact mechanism of how K1 causes hyperplasia and lymphomas in K1-expressing mice is not known. The cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM) of K1 was previously shown to be involved in activation of nuclear factor-kappa B (NF-κB). Moreover, we have recently shown that K1 suppresses Fas-mediated apoptosis through its extracellular immunoglobulin-like domain and that K1-transfected mice survive a lethal dose of agonistic anti-Fas antibody (Jo2). We thus hypothesized that development of hyperplasia and lymphomas in K1-expressing mice is driven by alterations in Fas signaling.

Results

Gross examination of thoracic and abdominal cavities of transgenic mice with K1 expression driven by a ubiquitous promoter, which were sacrificed at 18 months of age, revealed enlarged cervical, mediastinal, renal, and mesenteric lymph nodes and spleens. Peyer patches were also enlarged and readily visible on the outer surface of the ileum. Out of 10 K1 mice, 90 percent developed lymphoid hyperplasia (> 3 mm) and 60 percent developed lymphomas, while all (26) control mice remained hyperplasia- and lymphoma-free. In the extreme cases, K1 mice developed liver or mesenteric tumors (four and four out of 10 mice, respectively). Spleens of 78 percent of K1 mice were enlarged at 18 months and were on average 3.5 times heavier than spleens of non-expressing control mice (332 ± 200 mg versus 94 ± 26 mg, $P < 0.03$). Hematoxylin and eosin staining of spleen sections showed expansion to the periarteriolar lymphocyte sheath with disruption of normal follicular architecture. Staining of spleen sections with anti-kappa and anti-lambda light chain antibodies revealed the presence of monoclonal foci in three out of three K1 mice (average six foci per single section of spleen), but none in the four control mice. Moreover, K1 protein was expressed in about 10 percent of splenic cells as judged from staining with anti-K1 antibody 2H5. To test the hypothesis that expression of K1 protein in spleens renders them resistant to Fas-mediated apoptosis, splenic cells of 6-month-old K1 mice (n = 3) and matched controls (n = 3) were isolated and incubated with 50 ng/mL of agonistic anti-Fas antibody Jo2. At 12 hours of treatment, only 4 ± 1 percent of splenocytes from K1 mice versus 17 ± 2 percent of control splenocytes were undergoing apoptosis ($P < 0.01$). At 24 hours of treatment, the difference was even more significant (11 ± 0.6% versus 50 ± 6%, $P < 0.005$). Splenocytes of K1 mice were indeed more resistant to Jo2-induced apoptosis than splenocytes from age-matched control mice. Of mice inoculated with a lethal dose of Jo2 antibody, three out of 12 K1 transgenic

(30%) and 13 out of 22 control mice (60%) died ($P < 0.05$), further confirming the protective effect of K1 against Fas-mediated apoptosis.

Conclusion

Overall, these results confirm that K1 is associated with lymphoid hyperplasia and lymphoma and provide a plausible explanation. Interference of K1 with Fas-mediated apoptosis disrupts the normal life cycle of lymphocytes.