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Human Herpesvirus 8 K1-Mediated Inhibition of Fas-Mediated Apoptosis Provides A New Insight Into Regulation of Fas Signaling

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Kaposi's sarcoma and primary effusion lymphomahave been linked to human herpesvirus 8 infection. Key to the pathogenesis of these cancers and the persistence of the virus is the transmembrane proteinK1, which induces lymphoproliferation and immortalization of lymphocytes throughunknown mechanisms. K1 transgenic mice showed expansion of the lymphoid system; enlarged spleens, lymph nodesnodes, and development of lymphoma and sarcoma tumors. The K1 splenocytes were resistant to apoptosis induced by agonistic anti-Fas antibody. We demonstrated that K1-mediatedinhibition of Fas agonist-inducedcaspase8-dependent apoptosis in transgenic mice did not require an immunoreceptor tyrosine-based activation motif (ITAM) of K1. K1 bound Fas through the immunoglobulin-like extracellular domain, and blocked apoptotic signaling via interference with the binding of FasLand subsequently suppressed formation of the death-inducing signaling complex.

We anticipated that the K1 mimics the function of endogenous proteins participating in regulation of Fas receptor signaling. To identify these proteins, we purified activation-resistant Fas protein complexes and identified nucleolin as protein associated with activation-resistant Fas. To confirm Fas-regulatory function of nucleolin, we over-expressed nucleolin in mouse liver where it blocked Fas-mediated apoptosis. On the other hand, nucleolin knockdown in cells enhanced the levels of Fas-mediated apoptosis by enhancing the binding of Fas ligand. These results are consistent with the role of other Fas receptor-binding proteins such as hepatocyte growth factor receptor and CD44that bind Fas and interfere with the initiation of Fas-mediated apoptosis.

These data reveal a novel mechanism of regulation of Fas-mediated apoptosis by a viral receptor-like protein and shed light on the other similar regulators of Fas apoptotic signaling.