Programmed cell death activates latent herpesviruses

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Researchers have found that apoptosis, a natural process of programmed cell death, can reactivate latent herpesviruses in the dying cell. The results of their research, which could have broad clinical significance since many cancer chemotherapies cause apoptosis, was published ahead of print in the *Journal of Virology*.

Human herpesviruses (HHV) are linked to a range of childhood and adult diseases, including chickenpox, mononucleosis, cold sores, and genital sores, and are of a particular concern for patients who are immunosuppressed due cancer or AIDS. Some HHV types are so common they are nearly universal in humans. A key feature of these viruses is their ability to remain latent for long periods of time, and then reactivate after the latent phase. Previously, reactivation was thought to be primarily due to waning immunity, immunosuppression, or exposure to certain inducing agents.

This study began when principal investigator Steven Zeichner of Children's National Medical Center and George Washington University in Washington, DC, followed up earlier findings that high concentrations of the antibiotic doxycycline can induce apoptosis, and can also activate replication by the Kaposi's Sarcoma-associated Herpesvirus (KSHV), and a study by his former mentor, Bernard Roizman of the University of Chicago, which showed that apoptosis also triggers replication of herpes simplex virus-1, which causes cold sores in the mouth.

"We decided to test… several additional human herpesviruses that cause

notable diseases and which have good latent infection cell line models, including human herpesviruses (HHV)-6A, =6B, and -7, and Epstein-Bar virus (EBV)," says Zeichner. That all of these herpesviruses were activated by apoptosis suggested that this mechanism might apply to all herpesviruses.

The clinical implications could be staggering. Some important cytotoxic cancer chemotherapeutic drugs, including doxorubicin, vincristine, and prednisone act in part by inducing apoptosis, according to the study. Additionally, treatment with glucocorticoids has been known to worsen Kaposi's Sarcoma. The investigators also note that herpesvirus activation has been associated with poor outcomes following bone marrow transplantation.

"Activation of herpesviruses in these states and disorders has previously been variably attributed to general immune suppression, suppression of specific arms of the immune system, and increased concentrations of inflammatory and activating cytokines," write the researchers in the article. "If this activation occurs in potentially damaging ways, then perhaps patients at risk for herpesvirus activation should be treated with antiviral medications in addition to antineoplastic cytotoxic chemotherapy.

Almost all humans are infected with HHV-6, and many are infected with the other aforementioned herpesviruses, as well as cytomegalovirus, oral and genital herpes, and Varicella zoster, the virus that causes chicken pox and shingles.

More information: A copy of the manuscript can be found online at bit.ly/asmtip0913b. Formal publication is scheduled for the October 2013 issue of *Journal of Virology*.