Clue found to Epstein-Barr virus' ability to form and sustain tumors

September 5 2006

Researchers at the University of Wisconsin School of Medicine and Public Health (SMPH) have found a viral target that opens the door for the development of drugs to destroy tumors caused by Epstein-Barr virus (EBV).

The finding, published in the Sept. 4 *Proceedings of the National Academy of Sciences Online*, identifies the activity of a critical segment of a viral protein required to sustain EBV-related tumors. The researchers found that when they blocked this activity, the virus life cycle was broken.

Often linked to infectious mononucleosis, EBV also causes cancers that kill 100,000 people around the world each year. The virus, which infects the immune system's B cells and causes them to grow, is directly responsible for Burkitt's lymphoma, an often-fatal malignancy affecting thousands of African children annually. It is also causally associated with at least four other kinds of human cancers, including Hodgkin's lymphomas, lymphomas in AIDS patients and organ transplant recipients as well as nasopharyngeal carcinomas.

The SMPH researchers, based at the McArdle Laboratory for Cancer Research, focused on a viral protein they had previously found to be necessary to keeping Burkitt's lymphoma cells alive and growing in culture. The protein, called Epstein-Barr nuclear antigen 1 (EBNA-1), is the only protein the virus makes in all EBV-positive tumors.

"We've been trying to identify specific functions of EBNA-1 that we could target therapeutically," says Bill Sugden, professor of oncology who has studied EBV for more than 30 years. "Our goal is to develop a successful anti-viral, anti-tumor therapy for all EBV-positive tumors."

In the current study, Sugden and his colleague of 20 years, Wolfgang Hammerschmidt, now based at the German National Research Center for Environment and Health, designed genetic experiments to mutate various segments of the 640 amino acids that make up the EBNA-1 protein, which is one of about 100 proteins EBV encodes. They then infected human B cells with EBVs carrying various mutant EBNA-1s.

The analysis showed that one 25-amino acid segment within EBNA-1 was responsible for the regulation of viral gene transcription, the first step in the process by which a gene's coded information is converted first into RNA and then into protein.

Mutating the unique segment of amino acids prevented EBNA-1 from transforming resting B cells into proliferating cells.

Under normal conditions, a cellular protein binds this 25-amino acid segment of EBNA-1, allowing transcription of viral and cellular genes regulated by EBNA-1 to occur. Hammerschmidt and Sugden are now trying to identify the cellular protein.

"If we can identify this protein, it will be easier for us to develop assays to screen for small molecules that will compete with the protein in binding to EBNA-1," Sugden says. "By preventing the cellular protein from binding with the segment, EBNA-1 will not be able to carry out its function and the tumor cells it sustains will die."

The goal, which Sugden expects is achievable, is to end up with a drug that kills only EBV-positive tumor cells and doesn't harm other tissues in

the body.

Source: University of Wisconsin