Study reveals new clues to Epstein-Barr virus

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Epstein-Barr virus (EBV) affects more than 90 percent of the population worldwide and was the first human virus found to be associated with cancer. Now, researchers from Beth Israel Deaconess Medical Center (BIDMC) have broadened the understanding of this widespread infection with their discovery of a second B-cell attachment receptor for EBV.

The new findings, which currently appear on-line in *Cell Reports*, reinforce current directions being taken in the development of a vaccine to guard against EBV, and raise important new questions regarding the virus's possible relationship to malaria and to autoimmune diseases.

"Our discovery that CD35 is an attachment receptor for EBV helps explain several previously unsolved observations," explains the study's senior author Joyce Fingeroth, MD, a member of the Division of Infectious Diseases at BIDMC and Associate Professor of Medicine at Harvard Medical School.

First discovered in the early 1960s, EBV is one of eight viruses in the human herpesvirus family. The virus affects nine out of 10 people at some point in their lifetimes. Infections in early childhood often cause no disease symptoms, but people infected during adolescence or young adulthood may develop infectious mononucleosis. EBV is also associated with several types of cancer, including Hodgkin's lymphoma, non-Hodgkin's lymphoma and nasopharyngeal carcinoma, and has been linked to certain autoimmune disorders.

"EBV was the first human virus that was discovered to be a tumor virus," explains Fingeroth. "In fact, individuals who have had infectious mononucleosis have a four times increased risk of developing Hodgkin's disease." After the initial infection, the EBV virus remains in a person's body for life.

To gain entry, viruses must first attach to their host cells. For herpesviruses, receptors on the viral envelope become connected to complementary receptors on the cell membrane. In the case of EBV, the virus gains access to the immune system by attaching to primary B cells.

Nearly 30 years ago, Fingeroth and her colleagues discovered that this attachment occurs via the CD21 protein, which until now was the only known B cell attachment receptor for EBV. The recent finding that B cells from a patient lacking CD21 can be infected and immortalized by EBV had indicated that an alternative attachment receptor must exist. The identification of this second receptor—CD35—by Fingeroth's team, led by first author Javier Ogembo, PhD, of BIDMC and the University of Massachusetts Medical School, not only underscores an important finding regarding primary infection but also underscores the importance of EBVgp350/220, (the virus protein that has been found to bind to both attachment receptors) for the development of a vaccine against EBV.

"The EBV glycoprotein gp350/220 is the most abundant surface glycoprotein on the virus," notes Fingeroth, adding that these results further suggest the virus fusion apparatus is the same for both receptors. "An EBV vaccine might be able to prevent infection or, alternatively, greatly reduce a person's risk of developing infectious mononucleosis and EBV-associated cancers, without necessarily preventing the EBV infection itself."

Interestingly, she adds, whereas a human has now been identified to be lacking the CD21 receptor, no persons are known to lack CD35.

"CD35 is a latecomer in evolution and in its current form, exists only in humans," says Fingeroth. "We know that it is often targeted in autoimmune diseases and was recently identified as a malaria receptor. Our new discovery may, therefore, reveal

new avenues for the exploration of unexplained links between EBV, autoimmune diseases, malaria and cancer."

Provided by Beth Israel Deaconess Medical Center