



Study Reveals How Epstein-Barr Virus May Lead to Cancer

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Chances are good that you've had an Epstein-Barr virus (EBV) infection, usually during childhood. More than 90% of us have, though we often don't know it. That's because most EBV infections are mild or produce no symptoms at all.

But in some people, EBV can lead to other health problems. The virus can cause infectious mononucleosis ("mono"), type 1 diabetes, and other ailments. It also can persist in our bodies for years and cause increased risk later in life for certain cancers, such as lymphoma, leukemia, and head and neck cancer. Now, an NIH-funded team has some of the best evidence yet to explain how this EBV that hangs around may lead to cancer.

The paper, [published recently in the journal Nature](#), shows that a key viral protein readily binds to a particular spot on a particular human chromosome. Where the protein accumulates, the chromosome becomes more prone to breaking for reasons that aren't yet fully known. What the study makes clearer is that the breakage produces latently infected cells that are more likely over time to become cancerous.

This discovery paves the way potentially for ways to screen for and identify those at particular risk for developing EBV-associated cancers. It may also fuel the development of promising new ways to prevent these cancers from arising in the first place.

The work comes from a team led by Don Cleveland and Julia Su Zhou Li, University of California San Diego's Ludwig Cancer Research, La Jolla, CA.

Over the years, it's been established that EBV, a type of herpes virus, often is detected in certain cancers, particularly in people with a long-term latent infection. What interested the team is a viral protein, called EBNA1, which routinely turns up in those same EBV-related cancers.

The EBNA1 protein is especially interesting because it binds viral DNA in particular spots, which allows the virus to persist and make more copies of itself. This discovery raised the intriguing possibility that the protein may also bind similar sequences in human DNA. While it had been

suggested previously that this interaction might play a role in EBV-associated cancers, the details had remained murky—until now.

In the new study, the researchers first made uninfected human cells produce the viral EBNA1 protein. They then peered inside them with a microscope to see where those proteins went. In both healthy and cancerous human cells, they watched as EBNA1 proteins built up at two distinct spots and confirmed that this accumulation was dependent on the protein's ability to bind DNA.

Next, they mapped where exactly EBNA1 binds to human DNA. Interestingly, it was along a repetitive non-protein-coding stretch of DNA on human chromosome 11. This region includes more than 300 copies of an 18-letter sequence that looks quite similar to the EBNA1-binding sites in its own viral genome.

What's more, the researchers noticed that the repetitive DNA there takes on a structure that's known for being unstable. And these so-called fragile sites are inherently prone to breaking.

The team went on to uncover evidence that the buildup of EBNA1 at this already fragile site only makes matters worse. In EBV-infected cells, increasing the amount of EBNA1 protein led to more chromosome 11 breaks. Those breaks showed up within a single day in about 40 percent of cells.

For these cells, those breaks also may be a double whammy. That's because the breaks are located next to neighboring genes with long recognized roles in regulating cell growth. When altered, these genes can contribute to turning a cell cancerous.

To further nail down the link to cancer, the researchers looked to whole-genome sequencing data for more than 2,400 cancers including 38 tumor types from the international [Pan-Cancer Analysis of Whole Genomes](#) consortium. They found that tumors with detectable EBV also had an unusually high number of chromosome 11 abnormalities. In fact, that was true in every single case of head and neck cancer.

The findings suggest that people will vary in their susceptibility to EBNA1-induced DNA breaks along chromosome 11 based on the amount of EBNA1 protein in their latently infected cells. It also will depend on the number of EBV-like DNA repeats present in their DNA.

Given these new findings, it's worth noting that the presence of EBV and [the very same viral protein](#) has been implicated also in [the link between EBV and multiple sclerosis \(MS\)](#). Together, these recent findings are a reminder of the value in pursuing an EBV vaccine that might thwart this infection and its associated conditions, including certain cancers and MS. And, we're getting there. In fact, an early-stage clinical trial for [an experimental EBV vaccine](#) is now ongoing here at the NIH Clinical Center.

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