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Epstein-Barr Virus Turns 50

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This month marks the 50th anniversary of the discovery of Epstein-Barr virus (EBV) as the first human tumor virus. In March 1964, a team led by Anthony Epstein identified herpesvirus-like particles in cultured tumor cells derived from African Burkitt's lymphoma tissue (1). At that time, the idea that a virus caused human cancer was met with some skepticism because the theory that cancer was infectious had been dismissed in the previous century. Stalwart investigators continued to track EBV until the viral culprit was declared a class I carcinogen by the International Agency for Research on Cancer and the World Health Organization in the late 1990s. Despite the consensus that EBV is a bona fide tumor virus, the mechanisms of cancer causation by EBV remain an area of active investigation and controversy 50 years since its initial discovery.

One of the most confounding findings relating to the association of EBV with rare cancers is that EBV prevalence in the normal population is extraordinarily high, reaching over 90% of the adult population worldwide. Because EBV is a member of the herpesvirus family, it is very adept at establishing a long-term latent infection. Exposure to EBV can be detected by serology, and latent forms of EBV can be readily detected by molecular methods in a small percentage of B-lymphocytes from healthy individuals. Furthermore, EBV was identified as a major causative agent of infectious mononucleosis, which seemed incongruent with its role in cancer causality. How could a relatively common virus be the cause of an endemic childhood cancer in Africa?

Viral causes of animal cancers had been known since 1911, when Peyton Rous discovered that retroviruses cause cancers in chickens. But it was not until the discovery in 1968 that viruses related to EBV were responsible for T cell lymphomas in nonhuman primates that the case for EBV-dependent tumorigenesis became more compelling. EBV was soon found to be highly efficient at transforming quiescent human B-lymphocytes into continuously proliferating lymphoblastoid cell lines (2), and EBV is now a common laboratory tool used to immortalize B-lymphocytes for human genetic studies. The search for additional cancers that contain EBV revealed that latent forms of the virus were present in most nasopharyngeal carcinomas endemic to Southeast Asia. Although EBV is found in ~100% of this cancer type, it was only found in a third of these carcinomas outside of endemic regions, similar to what was found for Burkitt's lymphoma (cancer of B-lymphocytes).

Half-century mark. Epstein-Barr virus was discovered 50 years ago. The details of its association with cancer remain enigmatic and an effective therapy has yet to be developed.

Fifty years after its discovery and its association with cancer, a vaccine or therapy for Epstein-Barr virus remains elusive.

These imperfect correlations fueled concerns that EBV was not a driver of oncogenesis but merely an opportunistic passenger in cancer, and that high correlations could be attributed to increase viral load in endemic regions.

The discovery of EBV as a causative agent of X-linked lymphoproliferative disease, a rare genetic disorder of immunologic dysfunction, illuminated the importance of host immunologic status in the control of viral-associated malignancies. Moreover, during the era of the HIV-AIDS epidemic and before successful antiviral therapies, the prevalence of B-cell lymphomas and Kaposi's sarcomas revealed the opportunistic nature of these malignancies. The massive depletion of CD4 T cells and immune dysfunction in HIV-AIDS is sufficient to unleash the potential of latent EBV to drive immunoblastic large B-cell lymphomas. The insight that immunosuppression could drive malignancy fueled the search for a causative agent for Kaposi's sarcoma, and led Yuan Chang and Patrick Moore to identify a second human gammaherpesvirus linked to human cancer (3). Kaposi sarcoma-associated herpesvirus (KSHV), also called human herpesvirus 8 (HHV8), has a near perfect correlation with all forms of Kaposi's sarcoma, and also with some B-cell malignancies, including pleural effusion lymphomas. The identification of KSHV as a second human tumor virus from the gammaherpesvirus field solidified the argument that these viruses have a causative role in human cancer.

Infectious agents in cancer were found to be more common than originally thought. In the early 1990s, *Helicobacter pylori* was shown to cause peptic ulcer diseases, a finding that was recognized with the 2005 Nobel Prize to Robin Warren and Barry Marshall. This finding opened the door to linking the bacterium with gastric carcinoma. Interestingly, EBV has been consistently found in ~10% of all stomach cancers and is now recognized as a distinct subtype of the cancer. The most compelling case for virus-associated cancer has been made for human papillomaviruses (HPVs) and cervical carcinoma. All forms of cervical carcinoma contain a subtype of HPV that corresponds to a high-risk viral genome. The distinction between low- and high-risk viral genomes provided one explanation for how a common virus could be associated with relatively rare forms of cancer. The high-risk strains of HPV are more likely to develop cancer. The discovery that HPV was the etiological agent of cervical and oral squamous cell carcinomas resulted in a Nobel Prize shared by Harald zur Hausen (2008). To date, the number of viruses or infectious agents associated directly or indirectly with human cancer etiology has grown to include the human hepato-cellular carcinoma viruses (hepatitis C and B viruses), T cell leukemia virus (human T-lymphotropic virus I and II), and the Merkel cell carcinoma virus. In all, it is estimated that infectious agents are responsible for one-fifth of all cancers (4).

In addition to being the first human cancer virus to be discovered, EBV was also the first large herpesvirus genome to be completely sequenced (1995), a project that helped launch the genomic era (5). Long thought to have a highly conserved genome with only two major subtypes, recent studies suggest that additional polymorphisms may explain the variation in cancer risk, similar to that observed in human papillomaviruses (6). The EBV genome encodes close to 100 open reading frames, several of which are expressed consistently in human cancers [EBV nuclear antigen 1 (EBNA1); latent membrane protein 1 (LMP1)], and some of which have growth-transforming activity and are essential for EBV immortalization

of B cells in vitro and tumorigenesis in animal models (LMP1, EBNA2, EBNA3C). Its mechanisms of viral subterfuge include encoding viral pirates of the B cell receptor, CD40-like coreceptors, and the Notch family of transcription regulators (7). The EBV genome also encodes over 20 microRNAs and other noncoding RNAs that are expressed at high amounts in human cancers and have tumorigenic properties, including the potential to be transmitted via exosomes to noninfected neighboring cells (8). EBV can adopt variant gene expression patterns that enhance its adaptability and help it to evade host immune recognition. EBV latent infection can also epigenetically suppress host tumor suppressor genes, providing a potential “hit and run” mechanism for viral oncogenesis (9).

Although there is a vaccine for HPV (10), none yet exists for EBV. At least one effort to develop a vaccine targeting the EBV glycoprotein gp350 was effective in reducing the incidence of infectious mononucleosis (11), but did not prevent the occurrence of latent infection, raising concern that the vaccine would not prevent most EBV-associated cancer. B-cell lymphomas arising from EBV have been successfully treated by adoptive immunotherapy (12), but this approach has proven labor intensive and technologically challenging. Thus far, there are no selective treatments for EBV-associated disease, although efforts are underway to develop both biological and pharmacological inhibitors of viral proteins and oncogenes. And as more diseases with potential links to EBV infection are revealed, such as multiple sclerosis and lupus erythematosus (13), the need for personalized therapies for treating EBV will continue to grow.

To date, EBV is estimated to be responsible for ~200,000 cancers worldwide (4). The U.S. National Institute of Health (NIH) recently called for a new initiative to reduce global cancer incidence, with EBV among the top candidates for future advances (14). Further clinical testing of the gp350 vaccine, as well as development of second generation vaccines and diagnostics to measure vaccine efficacy and cancer risk factors have been recommended by an NIH-sponsored panel (14, 15). Among the new generation of vaccines will be those that treat latently infected individuals with existing EBV-driven cancers as well as those that are at high risk for developing EBV-associated disease (e.g. solid organ transplant recipients). Any vaccine that stimulates strong and selective T cell response to EBV-positive tumor cells is likely to provide protection and therapeutic benefit. Hopefully the successes of HPV and hepatitis B virus vaccination programs will encourage new and ongoing efforts to find a suitable immunological or pharmacological treatment for EBV and associated disease. An efficacious antiviral would also provide the final confirmation that EBV is indeed a tumor-causing virus.

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