News Release

Title　Epstein-Barr virus lytic gene BNRF1 promotes B-cell lymphomagenesis via IFI27 upregulation

Key Points

- *Epstein-Barr virus (EBV) BNRF1 enhanced the frequency of tumor formation in a mouse xenograft model*
- *BNRF1 induced interferon-inducible protein 27 (IFI27) expression*
- *BNRF1-knockout or IFI27-knockdown induced reactive oxygen species (ROS) production*

Summary

A research group led by Professor Hiroshi Kimura and Associate Professor Yoshitaka Sato of the Department of Virology, Nagoya University Graduate School of Medicine, and their collaborators have demonstrated that the Epstein-Barr virus (EBV) BNRF1 induces host factor interferon-inducible protein 27 (IFI27), leading the infected cells to resilient growth and subsequently develop the tumor in a mouse xenograft model.
EBV-associated lymphomas are generally known to be resistant to anticancer drugs and have a poor prognosis. Effective treatments for these lymphomas need to be developed. Our finding is expected to lead to the development of new therapeutic methods targeting BNRF1 and IFI27 against Epstein-Barr virus-associated lymphomas.

Research Background

EBV is an oncogenic herpes virus that causes tumors in humans and was discovered about 50 years ago. More than 90% of adults are infected with this virus, but it shows almost no symptoms and establishes the latent infection in B cells. EBV occasionally causes various lymphomas such as Burkitt's lymphoma, diffuse large B-cell lymphoma, and post-transplant lymphoproliferative disorders.
EBV possesses more than 70 genes in the genome. The genes expressed in the latently infected cells have been intensively investigated. In addition to latent factors, accumulating evidence indicates that lytic replication, the process that generates new virus progeny by viral lytic proteins, contributes to cancer development. The role of the EBV lytic gene, BNRF1 in oncogenesis *in vivo* remains unclear.

Research Results

There are two types of human herpes viruses: those that cause tumors and those that do not. Although they share many genes, this study focused on EBV-BNRF1, a gene present only in tumor-associated herpesvirus, and analyzed the effect of this gene on tumor cells.

We generated a recombinant EBV (EBV/BNRF1-KO) lacking BNRF1 (EBV/BNRF1-KO) and infected it with B cells. The EBV/BNRF1-KO virus immortalized B cells, but its activity was lower than that of the wild-type (parental strain without any gene deletion) and the proliferative ability of infected cells was also reduced.

The EBV/BNRF1-KO infected cells failed to form tumors in the immunodeficient mice, indicating that loss of the BNRF1 gene significantly reduces the tumorigenicity of EBV.

Parallel RNA-seq analyses identified the host gene IFI27, which is affected by the expression of the viral factor BNRF1 gene. We showed that the growth phenotype of IFI27 knockdown is similar to that of BNRF1 knockout.

ROS were accumulated in EBV-infected cells by BNRF1 knockout or IFI27 knockdown, indicating insufficient energy production. Therefore, the BNRF1-IFI27 axis contributes to the robust growth of infected cells by suppressing the generation of ROS.

Research Summary and Future Perspective

In this study, we demonstrated the role of the EBV protein BNRF1 in the growth resilience of B-cells infected with EBV. BNRF1 induced the expression of IFI27, driving the proliferation of infected cells. IFI27 knockdown induced the overproduction of ROS, causing a fragile growth of both EBV-infected and EBV-transformed cells. Furthermore, disruption of the BNRF1-IFI27 axis reduced the pathogenicity of lymphoblastoid cell lines in a mouse xenograft model.

In diffuse large B-cell lymphoma, the presence of EBV in tumor cells is associated with a worse prognosis, and EBV-associated lymphomas are generally less responsive to anticancer drugs. Therefore, our findings provide insights into the neoplastic progression of EBV-infected cells and therapeutic targets against EBV-infected cells.

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Publication

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