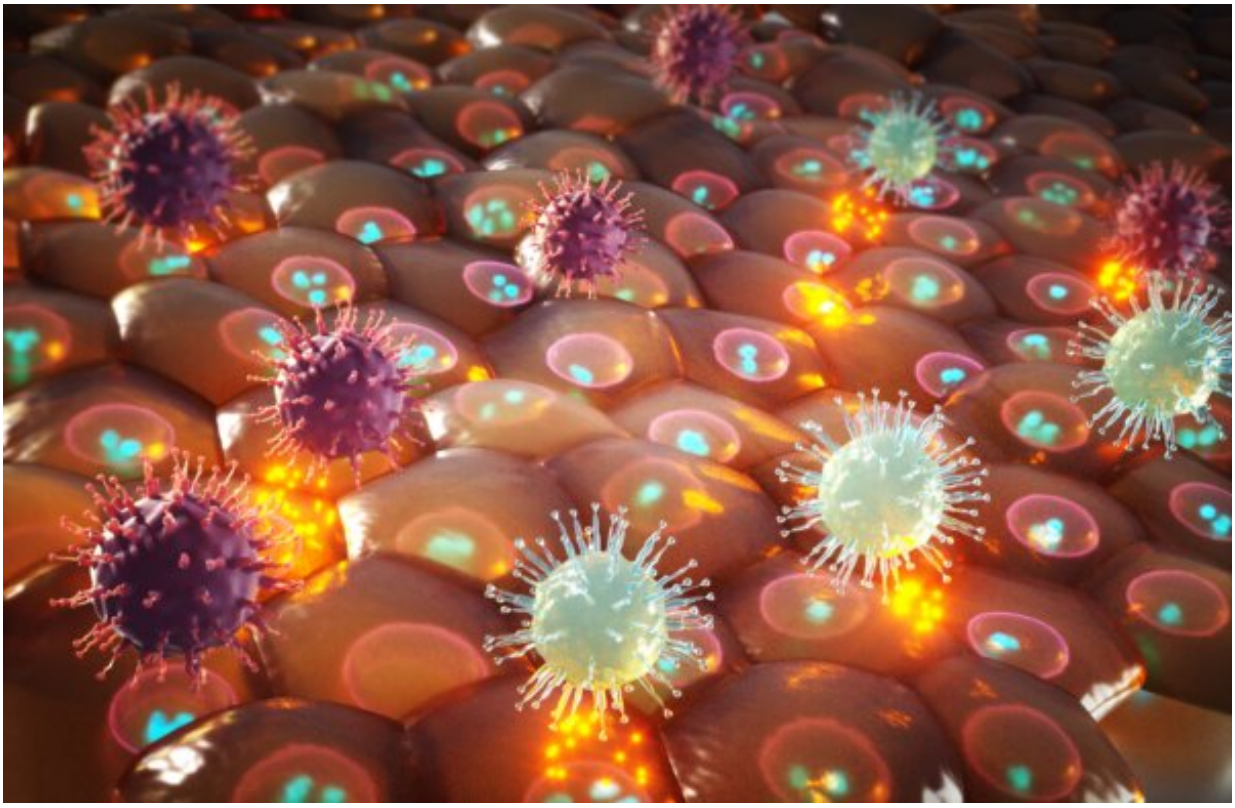
Scientists pinpoint protein that helps cancer-causing viruses evade immune response

February 6 2023, by Mark Derewicz



Viruses (EBV and KSHV) surrounding cells. Credit: Damania Lab

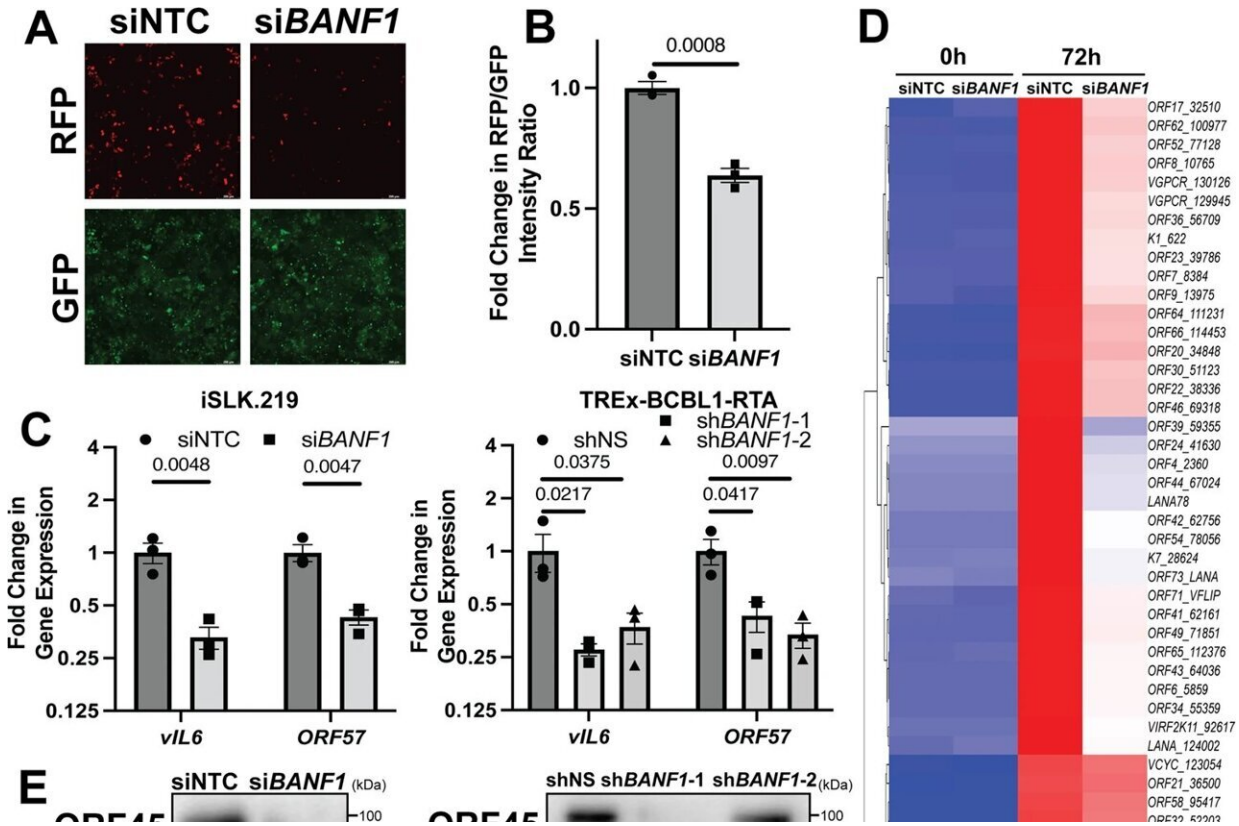
The viruses Kaposi sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV) have been linked to several cancers. For the first time, UNC School of Medicine scientists have discovered that these viruses use a human protein called barrier-to-autointegration factor 1, or BAF,

to evade our innate immune response, allowing the viruses to spread and cause disease.

These findings, published in *Nature Communications*, suggest that BAF and related proteins could be therapeutic targets to prevent these viruses from spreading and leading to cancers, such as Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, multicentric Castleman disease, nasopharyngeal carcinoma, and gastric cancer.

"Viruses are in a constant battle with the cellular immune system, which includes the protein cyclic GMP-AMP synthase, or cGAS, which binds to viral DNA and sounds the alarm to trigger immune responses and fight the viral invaders," said senior author Blossom Damania, Ph.D., the Boshamer Distinguished Professor of Microbiology and Immunology and member of the Lineberger Comprehensive Cancer Center. "We've discovered that KSHV and EBV use a different host cell protein, BAF, to prevent cGAS from sounding the alarm."

Viruses have evolved with humans for millions of years, so it's no surprise they've evolved tricks to evade our natural, or innate, immune responses. Finding out precisely how viruses do this is the basis for creating vaccines and therapeutics to overcome their tricks.



BAF is required for optimal KSHV reactivation from latency. iSLK.219 cells were transfected with non-targeting control (NTC) siRNA or *BANF1* targeting siRNA 48 h prior to the addition of 25 ng/mL doxycycline. TREx-BCBL1-RTA cells were transduced with lentiviral shRNA for 72 h prior to the addition of 1000 ng/mL doxycycline. **A** Fluorescent microscopy imaging of iSLK.219 cells for RFP and GFP signal at 72 h post-doxycycline treatment. **B** The fluorescence was quantified by plate reader. **C** Cells were harvested for RNA at 72 h (iSLK.219) or 96 h (TREx-BCBL1-RTA) post-doxycycline treatment and subsequent RT-qPCR was performed to quantify expression of viral mRNA transcripts. **D** iSLK.219 cDNA was prepared from cells harvested at 0 h and 72 h post-doxycycline treatment. Global KSHV gene expression profiling was performed. Data shown are the Z-score of the fold change ($2^{-\Delta\Delta Ct}$) over the geometric mean expression of three housekeeping genes averaged over two independent biological replicates. The heatmap was prepared using Partek Flow. **E** Cell lysates were prepared at 72 h (iSLK.219) or 96 h (TREx-BCBL1-RTA) post-doxycycline treatment and analyzed by western blotting with the indicated antibodies. **F** Cells were harvested and RNA isolated at 48 h post-siRNA

transfection and RT-qPCR was subsequently performed to quantify *BANF1* mRNA transcripts. **G** Cell lysates were prepared at 48 h post-siRNA transfection or 72 h post-shRNA transduction and analyzed by western blotting with the indicated antibody. *P* values are the result of two-tailed Student's *T* tests unless otherwise specified. Error bars indicate the standard error of the mean of three independent biological replicates. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-35898-2

In the case of KSHV and EBV, the expression of BAF is increased upon infection, suggesting that these viruses take advantage of this host protein to blunt the immune response to infection. In a series of experiments, Damania's lab found that BAF contributes to the degradation of the cGAS DNA sensor. With less cGAS protein available in the infected cell to detect DNA, the cells mount weaker immune responses, which allows these two viruses to replicate and spread more efficiently.

"BAF enables EBV and KSHV to reactivate from latency, replicate, and make more of themselves," said first author Grant Broussard, a graduate student in the Genetics and Molecular Biology Curriculum at UNC Lineberger. "Our study highlights the prominent role that DNA detection pathways like the cGAS pathway play in controlling viral infection."

He stressed that disrupting BAF activity with targeted therapies could reduce its immunosuppressive effects, thus restricting replication of these viruses to prevent the spread of disease.

Damania, who is a Leukemia and Lymphoma Society Scholar and a Burroughs Wellcome Fund Investigator in Infectious Diseases, added, "Preventing lytic replication will prevent transmission of these viruses and also reduce the global cancer burden associated with these two viruses."

More information: Grant Broussard et al, Barrier-to-autointegration factor 1 promotes gammaherpesvirus reactivation from latency, *Nature Communications* (2023). DOI: 10.1038/s41467-023-35898-2