Title: Development of a dual fluorescent reactivation reporter Epstein-Barr virus (DFRR-EBV) to optimize lytic-induction therapy of EBV-associated cancers

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Link: https://www.abstractsonline.com/pp8/#!/20273/presentation/834

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Scientific Abstract:

Epstein-Barr virus (EBV) is a highly successful γ-herpesvirus, infecting >95% of the human population. Approximately 0.01% of infected individuals will develop an EBV-associated cancer later in life, resulting in 200,000 annual cases globally. EBV-associated cancers, such as Diffuse Large B-Cell Lymphoma, are dependent on the expression of EBV latency genes for their continued growth and survival, making the disruption of latent infection a promising therapeutic target. “Lytic induction therapy” combines small molecules capable of reactivating EBV from latency with anti-viral drugs to increase toxicity to tumor cells and prevent EBV particle production. The full potential of this approach will require the development of second-generation lytic induction agents that induce a much greater proportion of tumor cells to enter the lytic cycle. Efforts to study the mechanisms of EBV reactivation are essential to this endeavor. EBV entry into the lytic phase is controlled by two viral transcription factors, Rta and Zta, and activators of the Rta and Zta promoters have previously been identified using reporter assays. These approaches, however, failed to capture major regulatory mechanisms that govern viral reactivation in EBV-positive tumors, such as long-range enhancer effects and epigenetic regulation of viral transcripts. To overcome these limitations, we constructed a dual fluorescent reactivation reporter virus (DFRR-EBV) that replaces Rta and Zta with GFP and RFP, respectively. This reporter is being used to screen a library of FDA-approved small-molecules to identify agents that reactivate EBV, in addition to a genome-wide unbiased CRISPR/Cas9 screen to identify negative regulators. Significantly, our reporter will distinguish between which small molecules are Rta versus Zta induction agents. Although Zta had been considered the principal regulator of the latent/lytic switch, we and others have demonstrated that expression of both Rta and Zta are essential for EBV reactivation1,2. Therefore, the combination of an Rta induction agent with a Zta inducer should act synergistically, offering a significant improvement over the current approach of single-agent lytic induction therapies for EBV-associated cancers.

References:

1. Ali, A. et al. Rta is the principal activator of Epstein-Barr virus epithelial lytic transcription. PLoS Pathog 18, e1010886 (2022).

2. Feederle, R. The Epstein-Barr virus lytic program is controlled by the co-operative functions of two transactivators. The EMBO Journal 19, 3080–3089 (2000).

Written Lay Abstract:

Epstein-Barr virus (EBV) is very common, and 95 percent of us have it in our bodies. Most people with EBV have no symptoms or may get sick with mono. In rare cases, EBV can lead to cancer because, when combined with changes in our DNA, it can change how healthy cells work. About 200,000 people in the world develop cancer related to EBV each year.

Researchers are looking for ways to treat cancers linked to EBV. Normally, EBV is latent in our body, which means it is not doing something inside our cells. A treatment called “lytic induction therapy” uses drugs to make the EBV virus activate to lyse (destroy) tumor cells with EBV and stops EBV from multiplying in our body. For this treatment to work well against cancer, researchers need to find a way to help destroy many more tumor cells.

There are two possible parts of the tumor cell destruction process related to EBV that researchers could target, called Rta and Zta. Researchers need to see how Rta and Zta work and lead to tumor cell destruction.

In this study, the researchers added markers in cells that would light up under a microscope when EBV was activated and Rta or Zta started the tumor cell destruction process. In the past, researchers thought that only Zta was needed for the process, but in this study the researchers found that both Rta and Zta are needed.

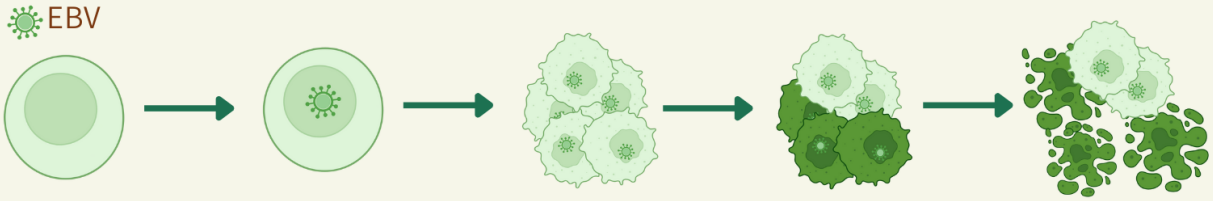
Findings from this study tell us that future lytic induction therapy for patients with EBV related cancer should use both Rta and Zta in the tumor cell destruction process.

Visual Lay Abstract:

Using Epstein-Barr Virus to Treat Lymphoma

Epstein-Barr Virus (EBV) is very common, and usually is latent (not active) and does not harm us. Sometimes, though, EBV is linked to cancer such as lymphoma.

Researchers want to know if we can activate EBV to lyse (destroy) cancer cells. This is called “lytic induction therapy”.



Healthy B-Cell, part of lymphatic immune system

EBV infects B-cell

Cancer of B-cell, lymphoma

Lytic induction therapy activates EBV in cancer cells

Cancer cells lyse (die) and cancer shrinks

Researchers found that lytic induction therapy activates EBV and two proteins called Rta and Zta help lyse the cancer cell.

Future lymphoma cancer treatments can use both Rta and Zta to improve lytic induction therapy.

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