

REVIEW

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## Epstein-Barr Virus (EBV) and the Effectiveness of Suberoylanilide Hydroxamic Acid (SAHA) as a Treatment for EBV Infection and Associated Cancers

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**Abstract:** Since being discovered in 1964, Epstein-Barr virus (EBV) has become a growing concern. Clinically, EBV is responsible for many diseases, most notably infectious mononucleosis. In addition to mononucleosis, EBV causes several cancers such as Hodgkin's lymphoma, Burkitt's lymphoma, and nasopharyngeal carcinoma (NPC). Suberoylanilide hydroxamic acid (SAHA) is an anti-cancer drug that inhibits growth and proliferation of various EBV-related cancers. SAHA acts as a histone deacetylase (HDAC) inhibitor. The responsiveness of SAHA treatment stems from the induction of EBV's lytic cycle.

**Keywords:** Suberoylanilide hydroxamic acid, Epstein-Barr virus, Hodgkin's Lymphoma, Burkitt's lymphoma, vorinostat

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*Advances in Tumor Virology* 2013:3 1–7

doi: [10.4137/ATV.S12242](https://doi.org/10.4137/ATV.S12242)

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## Introduction

The Epstein-Barr virus (EBV) is a  $\gamma$ -herpesvirus that was first characterized in 1964.<sup>1</sup> More than 95% of the world's population is seropositive for EBV. While most infected individuals show few symptoms, EBV is responsible for several diseases including infectious mononucleosis<sup>2</sup> and several B-lymphocyte cancers such as Hodgkin's lymphoma,<sup>3</sup> Burkitt's lymphoma,<sup>4</sup> and nasopharyngeal carcinoma (NPC).<sup>5</sup> EBV is an enveloped, lymphotropic double-stranded DNA virus. The virus is continually secreted through saliva and genital secretions for the remainder of an infected individual's life, enabling effective dispersion. There are two types of EBV—Types 1 and 2, or A and B—with Type 1 being more prevalent worldwide and Type 2 prevailing in Africa.<sup>6</sup> Once EBV enters an individual, it mainly infects B-cells and epithelial cells. The virus has a biphasic life cycle with both lytic and latent phases. EBV binds to B-lymphocytes through the interaction of viral gp350 protein and CD21.<sup>7</sup> Consequently, this interaction allows the viral protein gp42 to interact with MHC class II molecules, initiating endocytosis.<sup>8</sup> When infecting epithelial cells, EBV BRMF-2 protein binds to  $\beta 1$  integrin present on the cell membrane while the viral envelope protein gH/gL binds to epithelial  $\alpha \beta 6/8$  integrin.<sup>9</sup> In both B-cells and epithelial cells, the virus is engulfed via endocytosis. Once inside the cell, the viral envelope fuses with the engulfed vesicle, releasing the nucleocapsid into the host cell's cytoplasm where the nucleocapsid is subsequently dissolved. The genome is then transported into the cell's nucleus and replicated with a viral DNA polymerase.

During the lytic stage, the virus is actively replicating within B-lymphocytes and epithelial cells. There are three stages to lytic replication as defined by the expression of specific genes important for infection: immediate-early, early, and late. The immediate-early products are used as trans-activators for lytic replication. The early products perform functions including replication, metabolism regulation, and interference with antigen processing. The late products of viral replication encode structural proteins such as capsid proteins.<sup>10</sup>

Lytic replication ceases upon methylation of lytic genes and the virus enters the latent stage.<sup>11</sup> This stage is characterized by infection without active viral replication. Difference to lytic replication, EBV's DNA

genome forms a circular plasmid within the host cell's nucleus and the viral DNA uses the host cell's machinery rather than its own DNA polymerase to undergo genome replication.<sup>10</sup> During latency, EBV remains primarily in memory B-cells, which EBV previously caused to differentiate from normal B-cells.<sup>12</sup> Few viral genes are expressed. Those genes that are expressed encode different nuclear antigens (EBNA) and two latent membrane proteins (LMPs). Observing differential gene expression in different cell lines reveals that EBV undergoes three latency programs, with different pathologies resulting from each. Latent EBV virions can multiply in dividing memory cells (type I), trigger B-cell differentiation (type II), or activate naïve B-cells (type III). Each type of latency program plays a unique role in the development of various EBV-related cancers (Table 1).

EBV in the latency phase can be stimulated to re-enter the lytic replication stage. This allows the virus to infect other new B-cells or epithelial cells.<sup>12</sup> In vivo, the mechanisms that regulate re-entry into the lytic stage are not well described, but may be a result of the reaction of B-cells to unrelated infections.<sup>12</sup> Lytic replication can be artificially induced by the histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA), or vorinostat. SAHA has been shown to induce reactivation in epithelial malignancies<sup>13,14</sup> and has been approved by the Food and Drug Administration as a treatment for cutaneous T cell lymphoma.<sup>15</sup> This medication, which has already undergone regulatory approval, may be useful as a treatment for EBV-related cancers.

During the type II latency program, proteins LMP1 and LMP2 are expressed and cause cell proliferation

**Table 1.** EBV gene expression in latency and associate malignancies.

Latency type	Genes	Malignancies
Type I	EBER 1 & 2 EBNA 1	Burkitt's lymphoma
Type II IIa	EBNA 1 LMP-1	Hodgkin lymphoma NK/T cell lymphoma
IIb	EBNA 1–6	
Type III	EBNA 1–6 and LMP-1	Immunoblastic post-transplant or AIDS-lymphomas



observed in NPC and Hodgkin's lymphoma. The type III latency program is most often seen in cases of infectious mononucleosis.<sup>12</sup>

### EBV-related Infections

The most common EBV-related infection is infectious mononucleosis. Approximately a week after initial EBV infection, T-lymphocytes are primed to recognize the EBV replicative antigen which is present on the surface of infected B-cells. Once the T-cell has detected the infected B-cell, a cytotoxic response is initiated. Symptoms of mononucleosis typically begin with mild malaise. After a few days, flu-like symptoms arise, such as fever, sore throat, and mild fatigue.<sup>12</sup> In rare cases, infected individuals may develop hematologic complications, such as severe immune thrombocytopenia with petechiae, immune hemolytic anemia, and immune-mediated agranulocytosis, and chronic fatigue. An average case of infectious mononucleosis lasts about sixteen days. Recovery from mononucleosis is usually slow and often takes months.<sup>16</sup> Although infectious mononucleosis is not fatal, it remains the most common EBV-related disease at 500 cases per 100,000 individuals in the United States.<sup>17</sup>

EBV is also implicated in several types of cancer, most notably Hodgkin's lymphoma, NPC, and Burkitt's lymphoma. Hodgkin's lymphoma is a cancer of white blood cells. The exact relationship between EBV and Hodgkin's lymphoma is unclear.<sup>18</sup> Statistically speaking, it is improbable for cancer to arise in a cell already infected with EBV, as only about 1–100 cells per million of total B-cells are infected.<sup>18</sup> Immunohistochemical analysis of Reed-Sternberg cells, multinucleated cells associated with Hodgkin's lymphoma, have found EBV infection in approximately 50% of cases. This suggests that when other infections are coupled with an EBV infection, the chances of developing Hodgkin's lymphoma increase two- to four fold.<sup>19</sup> The EBV genome has been found in every Reed-Sternberg cell in EBV-positive tumors. The expressed genes correspond to type II latency program, specifically LMP1 and LMP2, and result in cell proliferation. LMP1 is capable of activating the CD40 pathway.<sup>20–22</sup> This pathway is normally involved in activation of B-cells by T-cells, causing increased cell proliferation.

EBV DNA has genes that encode for proteins expressed in both B-lymphocytes and epithelial cells

of the oropharynx, which are susceptible to NPC. Epstein-Barr Nuclear Antigen-1 (EBNA-1) is a protein encoded for by EBV DNA that is produced following infection which influences the development of this cancer. EBNA-1 is expressed in latently-infected B cells and binds to an EBV episome, a circular DNA plasmid. When EBNA-1 binds to an EBV episome, it regulates replication and allows the EBV genome to be maintained and replicated within B cells. More importantly, EBNA-1 is the only latent viral protein that cytotoxic T cells cannot recognize, thus providing protection from the immune system for the latently infected B cells.<sup>23</sup> The virus hijacks the host cell machinery and forces the production of viral proteins, inducing growth transformations in the host cell to begin the progression of tumor development. EBV episomes also encode for LMP and early antigens that aggregate on the surface of the host cell membrane. Additionally, several other signaling pathways are activated by the LMP to prevent apoptosis, such as the NF $\kappa$ B pathway.<sup>24</sup> Therefore, the latently infected B cell is now able to maintain EBV's genome, undergo rapid-uncontrolled cell division, and be protected from cytotoxic T cells and apoptosis. The combination of these events result in tumor growth as cell growth transformations increase and more B cells become infected within the oropharynx area.

Another EBV-associated lymphoma of B-cells is Burkitt's lymphoma. EBV is found in 98% of the cases of Burkitt's lymphoma in Africa. This is most likely due to the constant malarial exposure which may cause B-cells to proliferate, causing a high rate of the cancer.<sup>19</sup> For some EBV infections to induce cancer, a second event must occur such as mutation, environmental influence, or another viral infection. The frequent need for a second event explains why malaria is the most common infection that increases the risk of acquiring Burkitt's lymphoma. This relationship is especially evident in Africa with malarial infection reaching 219 million in 2010 according to the WHO.<sup>25</sup> However, in developed countries, EBV infection is not as prevalent, appearing in approximately 15% of Burkitt's lymphoma cases.<sup>18</sup> To diagnose Burkitt's lymphoma, a biopsy of the tumor mass is treated with antibody stains and titers; a poorly differentiated tumor of B cell origin is indicative of Burkitt's lymphoma. Burkitt's lymphoma is highly sensitive to

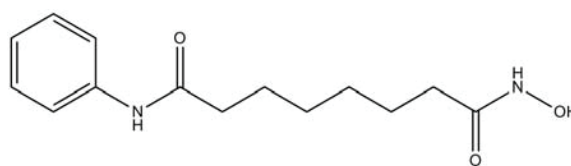
chemotherapy; if the cancer is caught at an early stage and treatment begins as soon as possible, the prognosis is good. In many cases, the tumor mass enters remission after one full cycle of chemotherapy treatment if started early enough.

In EBV-related Burkitt's lymphoma, EBV exhibits latency program I, mainly expressing EBNA-1.<sup>26</sup> The exact effect of this nuclear antigen in regards to Burkitt's lymphoma still remains unknown. Recent experiments have shown that EBNA-1 promotes cell survival which directly correlates to cancer progression.<sup>27</sup> Additionally, individuals with EBV-related Burkitt's lymphoma have unusually high titers of antibodies to early antigen (EA) and viral capsid antigen (VCA), which are associated with an increased risk for tumor development.<sup>18</sup>

Although Hodgkin's and Burkitt's lymphoma are EBV-related cancers of B-cells, NPC is an EBV-related cancer of epithelial cells. There are both undifferentiated and well-differentiated forms of NPC associated with EBV. NPC is found approximately 10 times more in individuals of southeast Asian descent than in other races and is found much more frequently in males than females. The symptoms that typically arise from NPC include cervical lymphadenopathy, eustachian tube blockage, and nasal obstruction with epistaxis.<sup>19</sup> In undifferentiated NPC, there are a high number of EBV episomes in each cell that parallels an increase in EBV antibody titers. In contrast, well-differentiated NPC have cells with a low number of EBV episomes and antibody titers are low.<sup>19</sup> IgA antibodies against EA and VCA are used in diagnosis and the monitoring of treatments.<sup>18</sup>

### Suberoylanilide Hydroxamic Acid (SAHA)

Cells infected with EBV in the latency phase demonstrate increased cellular proliferation, leading to an increased risk of malignancies. Thus, a treatment which involves the activation of the lytic stage in cancerous cells may result the death of cancer cells. SAHA is a HDAC inhibitor, which functions as a potent inducer of growth arrest, differentiation, and apoptotic cell death of transformed cells in vitro and in vivo (Fig. 1). SAHA has been proposed as a treatment for several cancers. The activity of HDAC enzymes results in decreased levels of transcription of specific genes by removing acetyl groups from specific lysine residues



**Figure 1.** Suberoylanilide hydroxamic acid (SAHA) acts as a histone deacetylase inhibitor. *Oncogene*. 2007;26:1351–1356. doi: 10.1038/sj.onc.1210204.

on histone proteins. In many cancers, HDAC activity is dysregulated, leading to increased expression of genes resulting in increased proliferation. X-ray crystallography demonstrates that SAHA binds to the active site of the *Aquifex aeolicus* HDAC-like protein, a close homolog of HDACs.<sup>28</sup> These data suggest that the aliphatic chain and the hydroxamic acid group of SAHA mimic the Lys side chain and acetyl group, respectively, of the normal substrate of HDAC. By inhibiting the activity of HDAC, transcription rates are increased. While there was no difference in histone acetylation between normal and transformed cell lines following SAHA treatment, tumor cell lines are ten times more sensitive to treatment.<sup>29</sup> Furthermore, mRNA and protein levels of the cell cycle kinase inhibitor p21<sup>WAF1</sup> increase nine-fold in bladder carcinoma cells following treatment with SAHA relative to normal cells.<sup>30</sup> p21<sup>WAF1</sup> expression is normally upregulated through the p53 pathway as a result of DNA damage, resulting in growth arrest.<sup>31</sup> HDAC inhibitors such as SAHA lead to the activation of p21 in a p53-independent manner.<sup>32</sup> Treatment with SAHA leads to the accumulation of reactive oxygen species (ROS) and the activation of caspases, leading to cell death in affected cells. In normal cells, levels of thioredoxin, a redox protein which scavenges for ROS, increased; this effect was not seen in cancerous cells.<sup>29</sup> This pathway results in cellular differentiation or apoptosis of cancerous prostate and nasopharyngeal cells in vitro and prevents tumor growth in vivo.<sup>14,33,34</sup> These results have led to studies showing SAHA showing positive results in either in vitro or clinical studies for prostate cancer,<sup>34</sup> breast cancer,<sup>35,36</sup> pancreatic cancer,<sup>37</sup> various leukemias,<sup>38</sup> colorectal cancer,<sup>39</sup> mesothelioma,<sup>40</sup> head and neck cancers,<sup>41</sup> as well as human immunodeficiency virus (HIV) infections<sup>42</sup> and in models of Huntington's disease.<sup>43</sup> In HIV, the virus remains latent in CD4<sup>+</sup> T-cells; this stage is not susceptible to highly active anti-retroviral therapy (HAART) and thus



patients will exhibit a rebound in viral load following cessation of treatment. SAHA has been suggested to activate the lytic cycle of HIV by the same mechanism of HDAC inhibition.<sup>42</sup> This leads to the lysis of CD4<sup>+</sup> cells with the HIV genome integrated into the genome and induces viral replication, which is susceptible to HAART. In 2006, SAHA (vorinostat, Zolinza) was given FDA approval for use as a treatment for cutaneous T-cell lymphoma, a form of skin cancer.

EBV exists in the latency phase during cancer. A proposed method of treatment for these cancers is to force EBV from its latent phase into its lytic phase. This causes cell lysis and ultimately the death of cancerous cells. SAHA is also speculated to influence apoptosis in cancerous cells of NPC, Burkitt's lymphoma, and gastric carcinomas at micromolar concentrations, with low levels of toxicity to the host.<sup>44</sup> The responsiveness of SAHA treatment stems from the induction of the lytic cycle of EBV, as observed in infected AGS/BX1 cell lines during EBV latency program II.<sup>44</sup> Research has found SAHA to be ineffective in inducing the lytic cycle of LCL329 cell lines during EBV latency program III and marginally effective in inducing AK2003 cell lines found during EBV latency program I.<sup>44</sup> AGS/BX1 cell lines exposed to SAHA during EBV latency program II had a higher prevalence of cellular degradation via apoptotic pathways than cells that were not exposed to SAHA. This may be attributed to the induction of EBV's lytic cycle. The AGS/BX1 cellular degradation was found to interrupt the cellular cycle. The disruption occurred in interphase between mitosis events and has been correlated to the induction of EBV's lytic phase. Furthermore, it was shown that reactivating the lytic phase causes G2/M arrest in EBV-infected carcinoma cells. The G2/M arrest is, therefore, directly correlated with the induction of the lytic cycle and will cause mitotic block in carcinoma cells.<sup>44</sup> SAHA was, however, able to induce EBV lytic cycle in HH514-16 BL, P3HR1, and Daudi cells.<sup>45</sup> It must be noted that SAHA has not been studied in all types of cancers; further studies are needed to elucidate the effectiveness of SAHA in various cancers.

## Conclusion

Since the EBV was discovered in 1964, it has remained a major concern. It is a herpesvirus that has evolved effective mechanisms of transmission. These effective mechanisms have allowed the virus

to infect more than 95% of the world's population. EBV infects both B-cells and epithelial cells and has a biphasic lifecycle. In most cases, infectious mononucleosis develops only a short time after infection. EBV has also been shown to be the causative agent in several cancers including Hodgkin's lymphoma, Burkitt's lymphoma, and NPC. To combat these cancers, many drugs that induce EBV's lytic cycle are being and studied. Currently, SAHA appears to be the most effective drug to induce EBV's lytic cycle and lead to cell death. EBV will continue to be a problem. However, with the development and testing of drugs like SAHA, its effect can be diminished. Future research regarding SAHA's mechanism of reactivating EBV's lytic cycle is critically important, and essential to effectively treat EBV-related cancers.

Several HDAC inhibitors have been identified that affect numerous pathways involving apoptosis, differentiation development, and epigenetics. Shirakawa et al reviews at least 18 different HDAC inhibitors.<sup>46,47</sup> SAHA has been shown to produce positive results when used to treat HDAC involved in prostate cancer,<sup>34</sup> breast cancer,<sup>35,36</sup> pancreatic cancer,<sup>37</sup> various leukemias,<sup>38</sup> colorectal cancer,<sup>39</sup> mesothelioma,<sup>40</sup> head and neck cancers,<sup>41</sup> as well as HIV infections<sup>42</sup> and in models of Huntington's disease.<sup>43</sup> Further studies are needed to determine if SAHA is effective against other specific HDACs and to determine the potential side effects of treatment.

## Acknowledgements

The authors thank Michael O'Reilly for contributing to the writing of the manuscript.

## Author Contributions

Conceived the concept: JDH. Wrote the first draft: SMB. Contributed to writing: TRJ, SMB. Developed the structure and arguments for the paper: JDH, SMB. Agree with the manuscript's conclusions: JDH, DJD, SMB, TRJ. Made critical revisions and approved the final version: JDH. All authors reviewed and approved the final manuscript.

## Funding

The authors would like to acknowledge the President's Mentorship Fund and the Alice Waters-Thomas Fund at the University of Pittsburgh at Johnstown.



## Competing Interests

Authors disclose no potential conflicts of interest.

## Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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