Contribution of Epstein–Barr Virus to Cancer Hallmarks

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The concept of ‘hallmarks of cancer’ was first introduced by Hanahan and Weinberg in 2000 and represented the cellular traits through which different cancers acquire the capabilities to survive, proliferate and disseminate. Epstein–Barr virus (EBV), the first recognized human oncogenic virus in history, is one of the environmental factors that can drive oncogenesis of several lymphoid and epithelial malignancies through various hallmarks of cancer. This entry summarizes the contribution of EBV lytic proteins to cancer hallmarks and provide a framework to address the complexity of EBV-driven oncogenesis.

Epstein–Barr virus (EBV) | lytic proteins | herpesvirus | oncovirus | cancer hallmarks

1. Overview of Cancer Hallmarks

The concept of ‘hallmarks of cancer’ was first introduced by Hanahan and Weinberg in 2000 and represented the cellular traits through which different cancers acquire the capabilities to survive, proliferate and disseminate. The six cancer hallmarks first described were evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, sustained angiogenesis, limitless replicative potential and tissue invasion and metastasis [1]. Two emerging hallmarks and two enabling characteristics, which included deregulating cellular energetics, avoiding immune destruction, genome instability and mutation and tumor-promoting inflammation, were appended to the previous conceptual framework in 2011 [2]. These enabling characteristics and emerging hallmarks support tumor progression [2]. Although the concept provided a seminal understanding on oncogenesis, arguments on the inclusion or exclusion criteria of some of the hallmarks emerged. A new definition was proposed by Fouad et al. in 2017 to incorporate evolutionary advantageous characteristics which promote the transformation and progression of phenotypically normal cells into malignant cells over time [3]. The former cancer hallmarks conceived by Hanahan and Weinberg were re-categorized into seven hallmarks, namely, selective growth and proliferative advantage, altered stress response favoring overall survival, vascularization, invasion and metastasis, metabolic rewiring, abetting microenvironment and immune modulation [3].

Hanahan added four new hallmarks in 2022, including two emerging hallmarks and two enabling characteristics, to address the increasing complexity of pathogenesis of cancer over time. They were non-mutational epigenetic reprogramming, unlocking phenotypic plasticity, polymorphic microbiome and senescent cells [4]. Cancer cells are capable of undergoing uncontrolled proliferation whereas the hallmarks of cancer are the means that lead to this phenotype. Normal cells can be transformed into cancerous cells by genetic and/or environmental factors. Oncogenic virus with strong epidemiological links to cancers is one of the environmental factors that can be

transmitted in utero, perinatally or postnatally. To date, seven oncogenic viruses, namely EBV, human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma-associated herpesvirus (KSHV), Merkel cell polyomavirus (MCV or MCPyV) and human T-lymphotropic virus type 1 (HTLV-1), have been identified [5].

Although different oncogenic viruses have their own unique strategies to drive oncogenesis, they have commonalities in hijacking certain cellular pathways. For example, HPV, EBV, HTLV-1, KSHV and MCPyV can modulate phosphoinositol 3-kinases (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) signaling pathway to affect cell growth, proliferation and survival. EBV LMPs facilitate cells in evading apoptosis and acquiring self-sufficiency in growth signals regardless of the availability of nutrients or ligand binding and overcome transforming growth factor beta-1 (TGF-β1)-mediated apoptosis [6][7]. Viral interleukin-6 (vIL-6), a KSHV-encoded cytokine, can unlock phenotypic plasticity of differentiated vascular endothelial cells through the PI3K/AKT pathway. AKT is activated upon vIL-6 binding to the gp130 receptor thereby upregulating prospero homeobox 1 (PROX1) to potentiate lymphatic reprogramming [8]. Oncoprotein E7 of HPV-16 enables cells to invade and metastasize by cytoplasmic retention of cyclin-dependent kinase inhibitor, p27, in a PI3K-AKT-dependent manner [9]. Tax oncoprotein of HTLV-1 activates AKT which phosphorylates forkhead box O3a (FOXO3a) and enables terminally differentiated CD4+ T cells to persist in order to disseminate HTLV-1 [10]. MCPyV small T (sT) antigen promotes hyperphosphorylation of 4E-BP1, a crucial downstream target of mTOR complex 1 (mTORC1), through the PI3K–AKT–mTOR pathway [11]. The above examples demonstrate the contribution of different viral oncoproteins to cancer hallmarks through a single host signaling pathway. An increasing number of studies had revealed the involvement of other viral oncoproteins in the establishment of cancer and defined the corresponding manipulated cellular pathways. Hence, viral-driven oncogenesis is vastly complex and new knowledge remains to be uncovered. A summary of how EBV proteins contribute to the cancer hallmarks is shown in **Figure 1**. As the functional studies of EBV gene products advance, a conceptual framework is needed to evaluate the contribution of the viral products to oncogenesis systematically.

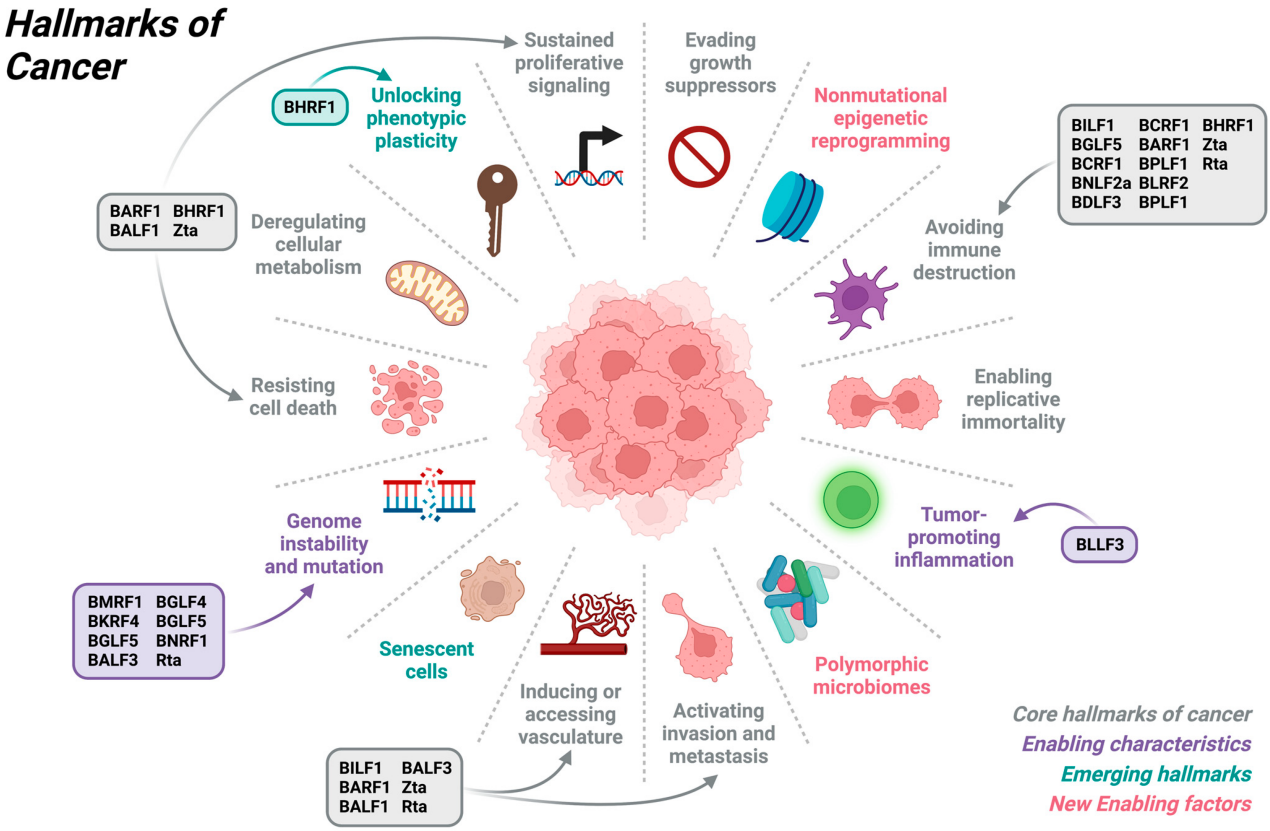

Figure 1. Contribution of EBV lytic proteins to hallmarks of cancers. EBV lytic proteins directly contribute to the hallmarks of avoiding immune destruction, activating invasion and metastasis, inducing or accessing vasculature, genome instability and mutation, resisting cell death, unlocking phenotypic plasticity and sustained proliferative signaling. Created with BioRender.com. Figure was adapted from “Hallmarks of Cancer: Circle” by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates, accessed on 23 February 2023.

2. Contribution of EBV to Hallmarks of Cancers

2.1. Avoiding Immune Destruction

Zta facilitates immune evasion via the downregulation of major histocompatibility complex (MHC) II by transcriptionally repressing immunomodulatory components, class II transactivator (CIITA) and cluster of differentiation (CD) *74* [12][13]. Rta, on the other hand, avoids immune destruction by decreasing interferon (IFN)-β production by suppressing the transcriptional activities of interferon regulatory factors (IRFs) 3 and 7 [14]. BHRF1 dampens innate immunity by inhibiting IFN-β induction through the mitochondrial antiviral signaling protein (MAVS)-stimulator of interferon genes (STING) signaling pathway [15]. Other EBV proteins that have immunomodulatory function are BGLF5, BILF1, BNLF2a, BDLF3, BCRF1, BARF1, BPLF1 and BLRF2. BGLF5 is an exonuclease that is able to modulate immune responses by downregulating the expression of MHC class I and II molecules impairing T-cell recognition as well as reducing toll-like receptor (TLR) 9 levels [16][17][18]. Similarly, BILF1, BNLF2a and BDLF3 disrupt antigen presentation mechanisms impairing CD8+ T-cell recognition of EBV-infected B-cells. BILF1 inhibits both innate and adaptive immune responses by internalizing and depleting MHC I from the cell

surface thereby reducing antigen presentation [19][20][21]. BNLF2a blocks the transporter associated with antigen processing (TAP) function, peptide loading and surface expression of MHC class I molecules [22]. BDLF3, a late lytic protein, evades CD8+ and CD4+ T-cell recognition by mediating ubiquitination on MHC molecules [23]. BCRF1 is a viral homolog of human IL-10 (vIL-10) which interferes with the antigen presentation mechanism of MHC class I molecule via downregulation of TAP1 [24][25][26][27][28]. BARF1 is a soluble hexameric glycosylated complex consisting of two immunoglobulin (Ig)-like domains and is detectable in the sera and saliva of NPC patients [29]. It acts as an allosteric decoy receptor that neutralizes and locks human colony-stimulating factor 1 (hCSF1) into an inactive conformation allowing cells to evade immune surveillance [30]. In addition to evading adaptive immune responses via similar mechanisms, BPLF1 and BLRF2 also facilitate evasion of innate immune responses. BPLF1 is a deubiquitylating enzyme (DUB) that suppresses TLR-mediated activation of nuclear factor kappa B (NF-κB) by deubiquitylating IκBα. [31]. BLRF2 inhibits type I IFN production via a cyclic GMP-AMP (cGAMP) synthase (cGAS)-STING pathway [32][33]. It binds to cGAS to inhibit its enzymatic activity and blocks cGAMP synthesis [32]. BPLF1 also deubiquitinates STING and TANK-binding kinase 1 (TBK1) and suppresses cGAS-STING and retinoic acid-inducible gene I (RIG-I)-MAVS pathways [34]. **Figure 2** displays the schematic diagram of the role of EBV lytic proteins in modulating immune responses related to oncogenesis.

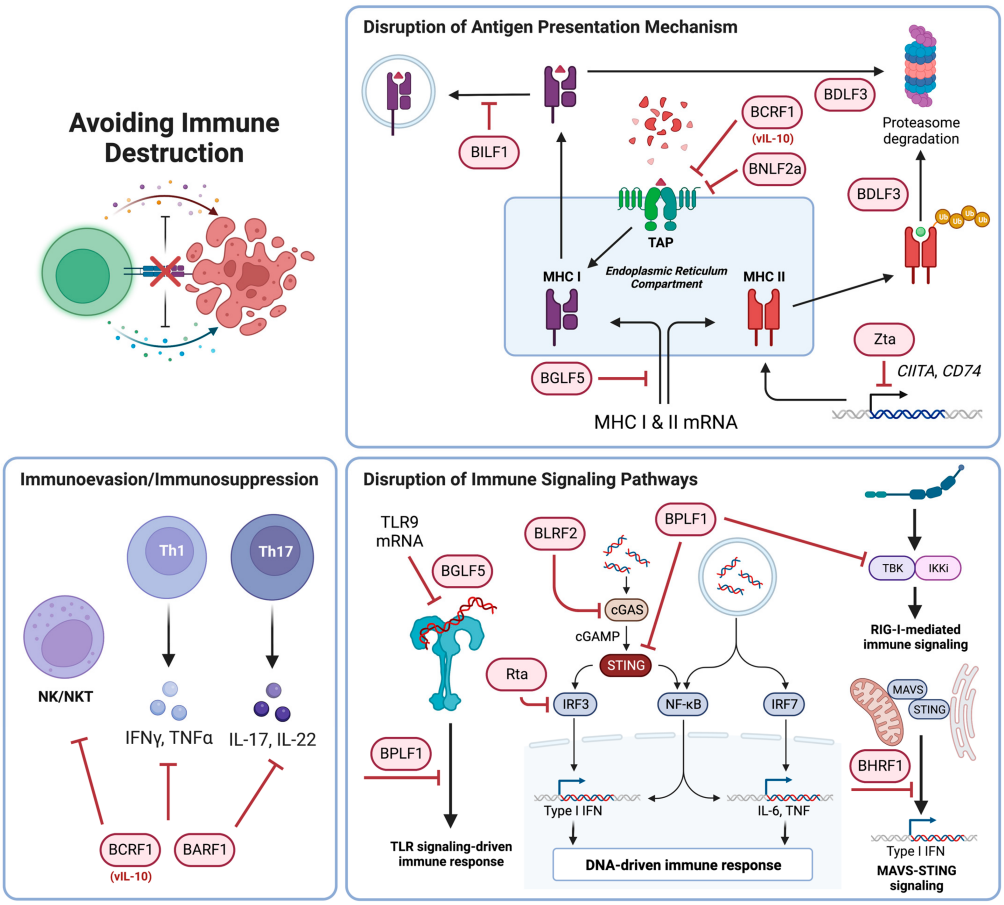

Figure 2. Schematic diagram of the mechanisms employed by EBV to evade immune responses. Zta, BGLF5, BILF1, BNLF2a, BDLF3 and BCRF1 avoid immune surveillance by modulating the antigen presentation mechanisms. BCRF1 and BARF1 are inhibitory molecules that facilitate immune evasion. Rta, BHRF1, BGLF5, BLRF2 and BPLF1 evade innate immune responses by modulating various components of immune signaling

pathways. Created with BioRender.com. Figure was adapted from “Icon Pack—Cytokine” and “cGAS-STING DNA Detection” by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates, accessed on 24 February 2023.

2.2. Activating Tissue Invasion and Metastasis and Inducing or Accessing Vasculature

Activating tissue invasion and metastasis as well as inducing or accessing vasculature are two closely related cancer hallmarks as they are usually modulated by secreted molecules associated with interconnected cellular pathways. Zta directly contributes to angiogenesis, invasion and metastasis via upregulation of cytokines, chemokines and growth factors such as IL-8, vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP) 3 and MMP9 [35][36][37][38]. Rta modulates the expression of IL-6 and MMP9 whose expression can lead to an increase in tumor invasiveness and metastatic properties [39][40][41]. Other lytic proteins, namely, BILF1, BARF1, BALF1 and BALF3, also contribute to these two cancer hallmarks. BILF1 induces angiogenesis and metastasis through VEGF secretion and intercellular adhesion molecule 1 (ICAM-1) expression [42][43]. BARF1 enhances migration and anchorage-independent growth in human embryonic kidney (HEK)-293 cells [29][44]. BALF1 transfectants exhibited higher rates of haptotactic migration in a transwell migration assay and formed more tumors of larger size in immunodeficient mice [45]. BALF3 expression could enhance metastasis as demonstrated by cell migration, cell invasion and spheroid formation assays [46]. **Figure 3** summarizes the roles of EBV lytic proteins in activating tissue invasion and metastasis and inducing or accessing vasculature in cancers along with other hallmarks including genomic instability and mutation, resisting cell death and sustained proliferative signaling.

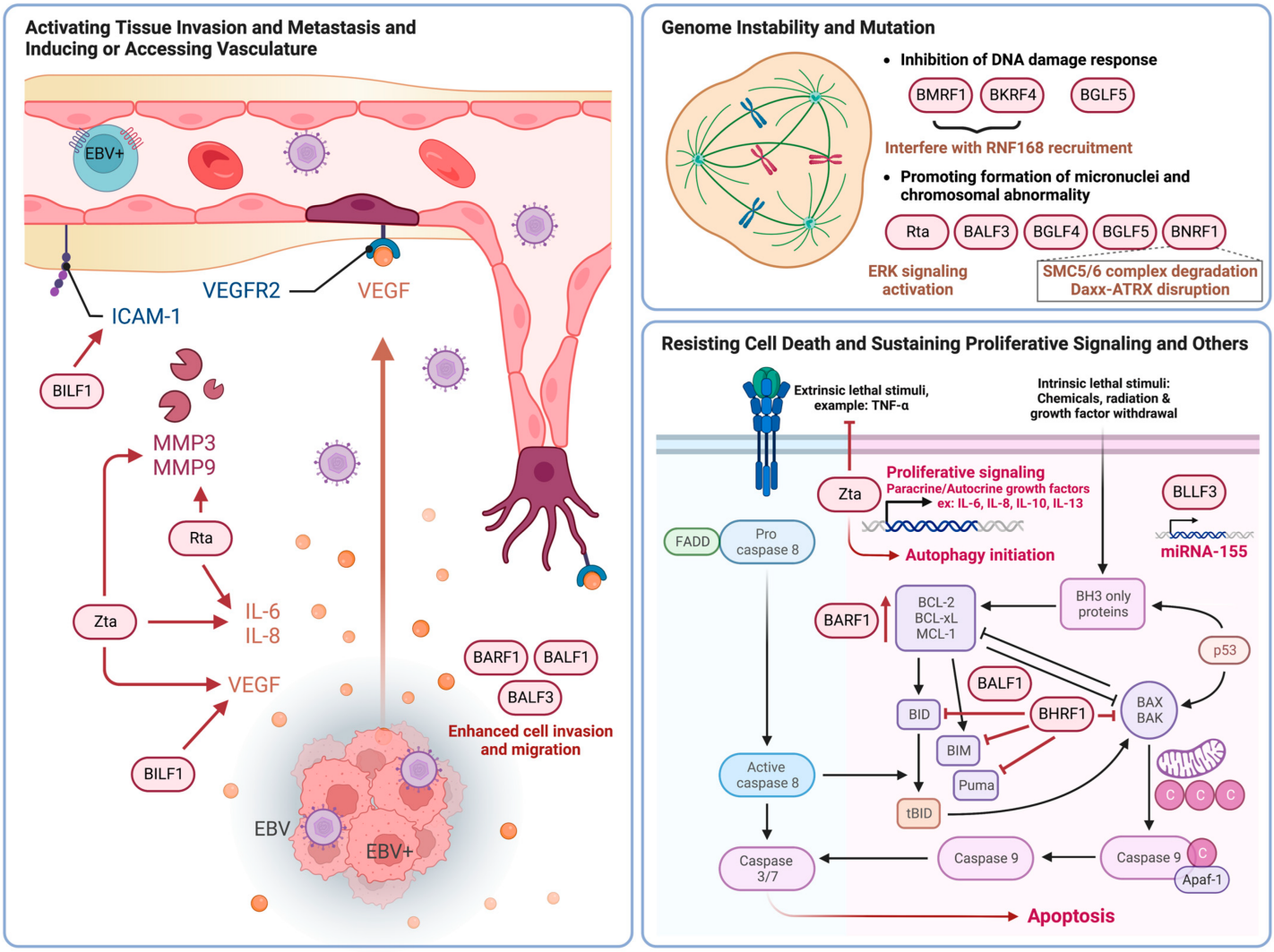

Figure 3. Schematic diagram of strategies of EBV in activating tissue invasion and metastasis, inducing or accessing vasculature, promoting genomic instability and mutation, resisting cell death and sustaining proliferative signaling. Zta, Rta, BILF1, BARF1, BALF1 and BALF3 induce tissue invasion, metastasis and angiogenesis. BMRF1, BKRF4, BALF3, BGLF4, BGLF5 and BNRF1 induce genomic instability and mutation through the inhibition of DNA damage response (DDR) and the formation of micronuclei and chromosomal instability. Zta, BARF1, BALF1 and BHRF1 promote cell survival via either cell death resistance or sustained proliferative signaling. Created with BioRender.com. Figure was adapted from “Tumor Vascularization” and “Extrinsic and Intrinsic Apoptosis” by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates, accessed on 24 February 2023.

2.3. Genome Instability and Mutation

The cancer hallmark of genomic instability and mutation can be induced by either inhibiting DNA damage response (DDR), repressing DNA repair, inducing DNA damage or interfering with chromosome integrity during cell replication. Early antigen protein D (EA-D), encoded by the BMRF1 gene, is the viral DNA polymerase processivity factor that functions as a transcriptional activator for some EBV and cellular genes [47][48][49]. BMRF1 suppresses DDR by inhibiting the recruitment of RNF168 and the ubiquitylation at double-stranded DNA (dsDNA) breaks [50].

Similarly, BKRF4 inhibits DNA repair and cell signaling associated with dsDNA breaks by binding to histones and blocking the recruitment of RNF168 [51]. In addition to these two proteins, BALF3, BGLF4 and BGLF5 also induce genetic alterations by promoting the formation of micronuclei and chromosomal abnormality, inducing DNA damage or DNA strand breaks and repressing the repair of DNA damage [46][52][53]. Moreover, Rta can induce genomic instability in epithelial cells by causing chromosome mis-segregation through the activation of extracellular signal-regulated kinases (ERK) signaling [54]. BNRF1 is another lytic protein that contributes to chromosomal aberrations by mediating the degradation of the structural maintenance of chromosomes (SMC) protein 5/6 (SMC5/6) [55][56]. Overexpression of BNRF1 can lead to aneuploidy [55]. In addition, it can also disrupt the formation of the DAXX-ATRX chromatin remodeling complex which potentially supports B-cell transformation [57].

2.4. Resisting Cell Death, Sustaining Proliferative Signaling and Other Cancer Hallmarks

A major characteristic of cancer lies in its ability to survive and proliferate owing to two related cancer hallmarks, namely, resisting cell death and sustaining proliferative signaling. BARF1 can activate B-cell lymphoma 2 (BCL-2) expression which leads to the elevation in the ratio of BCL-2 to BCL-2-associated X protein (BAX) and reduces Poly(ADP-Ribose) Polymerase 1 (PARP1) cleavage to protect the cells from apoptosis [58][59]. Other EBV proteins that have anti-apoptotic properties include BHRF1 and BALF1 which are Bcl-2 homologs [60][61][62]. Inhibition of pro-apoptotic proteins by BHRF1 was shown to facilitate chemoresistance and protect cells from apoptotic stimuli upon treatment with apoptosis-inducing agents [63]. BHRF1 also contributes to the cancer hallmark of unlocking phenotypic plasticity as epithelial cell differentiation is perturbed upon ectopic expression of BHRF1 in a human squamous cell carcinoma line [60]. On the other hand, BALF1′s role in inhibiting apoptosis may vary depending on the virus life cycle [61][64]. In addition, Zta can bind to the promoter of tumor necrosis factor (TNF) receptor 1 (TNFR1) and downregulate its expression to prevent TNF-α-induced apoptosis [65]. BLLF3, an EBV early gene encoding deoxyuridine triphosphate nucleotidohydrolase (dUTPase), facilitates tumor-promoting inflammation by inducing the expression of the miRNA-155 [66]. Virally induced miRNA-155 expression was shown to be critical for the growth of EBV-positive lymphoblastoid cell lines (LCLs) during latency [67]. In addition, BLLF3 induces inflammation by utilizing a TLR2-dependent mechanism to stimulate the release of pro-inflammatory cytokines such as IL-1β, TNF-α and IFN-ɣ [68][69][70][71].

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