AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology®

GEM

# MicroRNAs of Epstein-Barr Virus Control Innate and Adaptive Antiviral Immunity

**Manuel Albanese, Takanobu Tagawa, Alexander Buschle, Wolfgang Hammerschmidt**

Research Unit Gene Vectors, Helmholtz Zentrum München, German Research Center for Environmental Health and German Centre for Infection Research (DZIF), Partner site Munich, Munich, Germany

**ABSTRACT** Epstein-Barr virus (EBV) has established lifelong infection in more than 90% of humanity. While infection is usually controlled by the immune system, the human host fails to completely eliminate the pathogen. Several herpesviral proteins are known to act as immunoevasins, preventing or reducing recognition of EBV-infected cells. Only recently were microRNAs of EBV identified to reduce immune recognition further. This Gem summarizes what we know about immunomodulatory microRNAs of herpesviruses.

**KEYWORDS** cancer, human herpesviruses, immune evasion, immune surveillance, microRNA

**Accepted manuscript posted online** 7 June 2017

**Citation** Albanese M, Tagawa T, Buschle A, Hammerschmidt W. 2017. MicroRNAs of Epstein-Barr virus control innate and adaptive antiviral immunity. J Virol 91:e01667-16. https://doi.org/10.1128/JVI.01667-16.

**Editor** Felicia Goodrum, University of Arizona



Address correspondence to Wolfgang Hammerschmidt, hammerschmidt@helmholtz-muenchen.de.

M.A. and T.T. contributed equally to this article.

Epstein-Barr virus (EBV) is a successful human herpesvirus that infects about 90% of the human population. Upon infection, EBV reprograms resting, quiescent B lymphocytes, the main reservoir of this virus, to become activated, antigen-presenting cells, which become targets of the host's immune surveillance. EBV nonetheless can establish a latent lifelong infection in the memory B cell compartment, in part through its virally encoded immunoevasins, i.e., proteins that fend off both the innate and adaptive immune responses of its human host (1).

MicroRNAs (miRNAs) are small regulatory RNAs of 19 to 22 nucleotides (nt) in length. They usually bind to 3′ untranslated regions (UTRs) of targeted mRNAs, affecting their stability. Downregulation is often modest (<50%), and miRNAs are thought, therefore, to "fine-tune" gene expression (2). Single miRNAs can potentially target hundreds of different mRNAs, because the minimal requirement to bind the target mRNAs is the 6-nt-long "seed" sequence. Similarly, single mRNAs can be bound and regulated by multiple miRNAs forming a complicated regulatory network. Human miRNAs are involved in a wide range of physiological functions, such as development, growth, differentiation, apoptosis, stress response, and immune regulation (2, 3).

EBV was the first virus found to encode miRNAs (4, 5) and is the largest reservoir of miRNAs among human herpesviruses known to date. EBV encodes at least 44 miRNAs, which can potentially regulate hundreds of genes, but their identity is just beginning to emerge. EBV miRNAs are expressed in all phases of its complicated life cycle as well as in EBV-associated tumors (6). Accumulated evidence has shown that EBV miRNAs promote survival and proliferation of infected B cells early during infection as well as in tumor cells (7–10), but viral miRNAs were also found to modulate immune evasion (11, 12). Viral miRNAs in different herpesviruses are rarely conserved (13), but some regulate the same targets (14, 15).

In this Gem, we focus on miRNAs of EBV and other human herpesviruses and their recently identified functions in regulating innate and adaptive immune responses (Fig. 1). We also discuss the potential roles of circulating viral miRNAs and their possible implications in clinical practice.

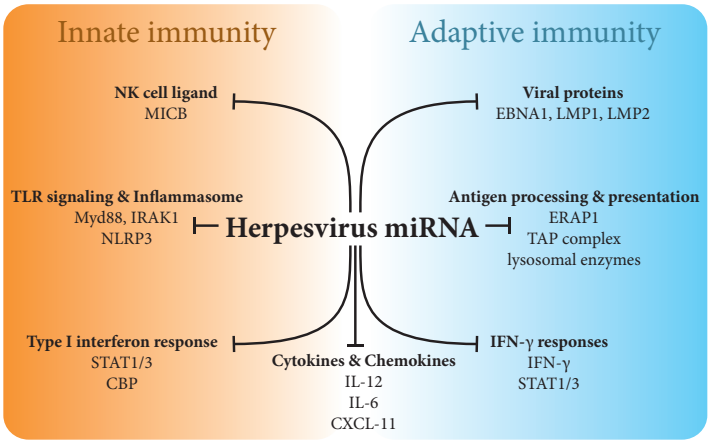


**FIG 1** Immunoevasive functions of herpesviral miRNAs. miRNAs of the human herpesviruses EBV, KSHV, and CMV target cellular and viral genes regulating the antiviral responses of innate and adaptive immunity. Shown are key genes downregulated by viral miRNAs. TLR, Toll-like receptor.

## VIRAL miRNAS AND INNATE IMMUNITY

Innate immune responses form the first line of defense against infectious agents, but viral miRNAs target several cellular transcripts in this pathway to escape immediate detection (Fig. 1). Type I interferons (IFN), secreted in response to viral infection, play a central role in antiviral immunity. They activate STAT transcription factors, which in turn induce the transcription of IFN-stimulated genes (ISGs) in infected and neighboring cells, leading to multiple antiviral functions. Diverse herpesviral miRNAs target components of the type I IFN signaling pathway, including STATs (16, 17), limiting the antiviral effects of ISGs.

Another important component of innate immunity is natural killer (NK) cells, which sense different activating and inhibitory molecules on the surface of stressed or virally infected cells. When induced upon stress, the major histocompatibility complex (MHC) class I polypeptide-related sequence B (MICB) surface molecule activates NK cells by binding to its receptor natural killer group 2D (NKG2D) (18). Several miRNAs of human herpesviruses, including EBV, Kaposi's sarcoma-associated herpesvirus (KSHV), and human cytomegalovirus (HCMV), have been reported to control the *MICB* transcript, reducing NK cell recognition and killing of virally infected cells (14, 19).

The regulation of inflammation is a common goal of viral miRNAs. Cytokine synthesis is regulated by EBV miRNAs upon infectious stimuli in nasopharyngeal cancers (NPC) (20) as well as by KSHV miRNAs in lymphomas (21). Human miR-155 regulates inflammation by Toll-like receptor signaling pathways. By targeting SHIP1/SOCS1 and TAB2, miR-155 can exert positive and negative effects on the proinflammatory responses to an invading pathogen, respectively (3, 22). Interestingly, KSHV miR-K12-11 mimics this human miRNA (15), and EBV also induces miR-155, because the latent membrane protein 1 (LMP1) of EBV activates its expression (23). Conversely, LMP1 itself is a direct target of several EBV miRNAs (24, 25), suggesting that they reduce or limit LMP1 signaling and may thus fine-tune innate immune responses directed against EBV.

## VIRAL miRNAS AND ADAPTIVE IMMUNITY

Among the main components of the adaptive immune response are T cells and antigen-presenting cells (APCs). Antigen presentation of viral peptides by APCs, i.e., EBV-infected B cells, is a multistep process and viral EBV miRNAs interfere with these steps to reduce the immunogenicity of infected cells. Cytokines and chemokines enhance adaptive immune responses, and herpesviruses appear to use their miRNAs to reduce the inflammatory microenvironment of infected cells as well (Fig. 1).

**Levels of viral antigens.** Controlling the abundant expression of viral genes can be a strategy of viral miRNAs, thus limiting levels of viral antigen. As a first example, simian

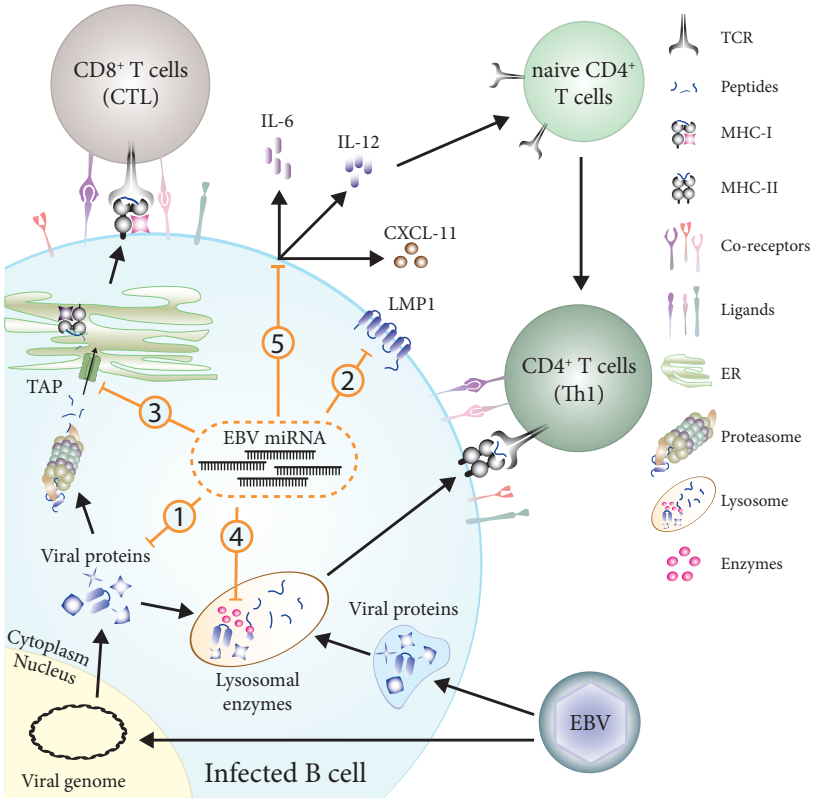


**FIG 2** EBV miRNAs globally control antiviral adaptive immune responses in infected cells. Upon infection, the viral DNA genome circularizes, and viral coding and noncoding RNAs are expressed immediately. EBV miRNAs support the evasion of adaptive immunity at several levels. 1, Viral miRNAs downregulate viral transcripts to limit viral antigen synthesis: miR-BART22 controls LMP2A/B, several BART miRNAs control LMP1, and EBNA1 is controlled by unidentified viral miRNAs; 2, reduced levels of LMP1 may lead to lower levels of antigen presentation because LMP1 activates coreceptors and MHC expression; 3, viral miRNAs control antigen processing for MHC class I-mediated presentation regulating the expression of TAP2, a target of miR-BHRF1-3 and -BART17; 4, miR-BART1 and -BART2 control the expression of the lysosomal enzymes IFI30 and LGMN, respectively; a third lysosomal enzyme, CTSB, is controlled by both miR-BART2 and -BHRF1-2, reducing the capacity to present antigenic epitopes on MHC class II molecules to $CD4^+$ T cells; 5, secretion of the NK cell ligand CXCL-11 is reduced by miR-BHRF1-3 while the mRNA encoding inflammatory cytokine IL-12 (and two additional cytokines, IL-12B and IL-23) is directly bound by five EBV miRNAs, resulting in suppressed Th1 differentiation. Other inflammatory cytokines, such as IL-6, are also reduced by viral miRNAs.

virus 40 (SV40)-encoded miRNAs were found to reduce SV40 T antigen expression, protecting infected cells from T cell recognition (26). Similarly, EBV miRNAs have been reported to target several viral genes downregulating them. Viral miRNAs limit the expression of the EBV proteins EBNA1 (25), LMP1 (27), and LMP2A/B (28) in infected B cells early after infection (Fig. 2). EBNA1 is required to maintain the viral genome in infected cells and to distribute genomes equally to daughter cells in mitosis. This protein is commonly expressed during latent infection and has the intrinsic ability to prevent processing and presentation of its epitopes on MHC class I molecules (29). Nevertheless, EBNA1 is a target of effector T cells, but viral miRNAs also limit EBNA1's immunogenicity, reducing its protein levels (25). These findings suggest that viral miRNAs can act as immunoevasins not only in lytic but also in latent infection.

**Antigen processing and presentation.** Recently, herpesvirus miRNAs were found to regulate cellular genes involved in antigen processing and presentation. HCMV miRNA miR-US4-1 was reported to control MHC class I antigen presentation by targeting ERAP1 (30), but this finding is controversial (31). ERAP1 is an aminopeptidase that optimizes peptide-MHC class I binding, and its downregulation leads to a reduced killing of infected cells by virus-specific T cells (30). We reported that EBV miRNAs also

regulate antigen processing and epitope transport in infected primary human B cells (25, 27), downregulating the transporter associated with antigen processing (TAP) complex and lysosomal enzymes affecting MHC class I- and class II-mediated epitope presentation, respectively (Fig. 2).

EBV miRNAs not only reduce the processing but also interfere with the presentation of viral antigens. We observed that cell surface MHCs and costimulatory molecules, necessary components for effective antigen presentation, are decreased by viral miRNAs. MHC and costimulatory molecules do not seem to be direct targets of viral miRNAs (25, 27) (Fig. 2), but these surface molecules might be under the control of LMP1, which is limited by several EBV miRNAs (24, 25, 44). LMP1 mimics CD40 signals in B cells and thus induces MHCs and costimulatory molecules; LMP1 downregulation by viral miRNAs reduces the immunogenicity of EBV-infected cells. It thus appears that several viral miRNAs balance LMP1 expression during latent infection in B cells.

**Controlling chemokines and cytokines.** Several chemokines and cytokines that regulate antiviral inflammatory responses are targets of multiple viral miRNAs. EBV miR-BHRF1-3 targets *CXCL11* (32), a chemoattractant of T cells, and thus may reduce local inflammation and T cell recruitment (Fig. 2). After EBV infection, primary B cells secrete various inflammatory cytokines, including interleukin-6 (IL-6) and IL-12. We found reduced levels of these cytokines in B cells expressing EBV miRNAs early in infection. At least five viral miRNAs directly target IL-12p40 transcript, hence reducing the secretion of IL-12 and IL-23, both being members of the IL-12 family, from infected B cells. The best known function of IL-12 is promoting the differentiation of naive $CD4^+$ T cells to antiviral Th1 cells, a function inhibited by EBV miRNAs (27) (Fig. 2).

In the lytic phase during *de novo* virus synthesis, multiple viral proteins are expressed that act as immunoevasins to protect the cells from virus-specific effector T cells. During the early days of infection in the prelatent phase, comparatively few viral immunomodulatory proteins are expressed (33). During this early phase and presumably also during latency, EBV uses its many nonimmunogenic miRNAs as alternative immunoevasins to protect the virus-infected cells from adaptive immune responses.

## CIRCULATING VIRAL miRNAS

Extracellular, circulating miRNAs in the bloodstream are considered potential biomarkers as a result of their disease-specific expression patterns. Circulating miRNAs of EBV have been proposed to serve as diagnostic markers in patients with nasopharyngeal carcinoma, for example (34).

The biological functions of circulating viral miRNAs are under investigation. EBV miRNAs contained within extracellular vesicles (EVs) were reported to be released constantly from lymphoblastoid B cell lines (35, 36). EVs can be taken up by different cell types, including monocytes and monocyte-derived dendritic cells (35), plasmacytoid dendritic cells (37), and epithelial cells, mainly via caveola-dependent endocytosis (38). Transfer of viral miRNAs to cells can lead to the repression of target genes (35); for example, miR-BART15 represses the inflammasome protein NLRP3 in a monocytic cell line (39). The putative functions of EV-contained miRNAs are controversial, because their abundance in EVs is low (40). Interestingly, infectious EBV particles also contain miRNAs (41), suggesting that they can be passively delivered, i.e., transduced during infection to exert so far unknown but perhaps immunoevasive functions in recipient cells.

## OUTLOOK

EBV expresses viral miRNAs in the prelatent phase immediately after infection, during latency, and in the lytic, productive phase. Particularly in the prelatent and latent phases, when the expression of viral immune evasion proteins is limited, the many viral miRNAs are likely to have important immunoevasive functions. Viral miRNAs are nonimmunogenic and are transcribed and processed like miRNAs of the cellular host. EBV and other herpesviruses (except betaherpesviruses such as cytomegalovirus) en-

code miRNAs in gene clusters, ensuring their simultaneous expression and potential cooperative functioning. The IL-12 and the STAT1 signaling pathways, which are targeted by multiple miRNAs encoded by EBV or KSHV, respectively, are revealing examples of the potential of viral miRNAs to repress single genes or pathways, a function that goes well beyond the fine-tuning of single genes.

In this light, it is remarkable to learn that miRNAs of different members of the herpesvirus family are distinct, sharing little sequence conservation, with few exceptions (15, 42). Lack of sequence conservation imposes a general difficulty for researchers because conservation across species is one of the best parameters to predict the targets of miRNAs. Instead, each herpesvirus has evolved its own set of miRNAs, probably to adapt to the RNA synthetic networks in the different cell types human herpesviruses infect. miRNAs of different herpesviruses rarely target the identical transcripts in the different host cells but rather alter the same global functions, such as antiviral immunity.

During infection, herpesviruses use their miRNAs to evade immune surveillance by the host. EBV-associated tumor cells also express viral miRNAs (6), and it seems plausible that they also reduce the anti-tumor response of infiltrating immune cells. Several strategies have been developed recently to block miRNA functions directed at indications other than EBV-associated diseases, and some have reached the phase of clinical studies (43). If successful, similar blocking of viral miRNAs in EBV-associated tumors may restore functional anti-tumor immunity and thereby benefit patients with these tumors.

## ACKNOWLEDGMENTS

We apologize for not citing all relevant work due to space constraints.

We thank Bill Sugden and Andreas Moosmann for critical readings of the manuscript and valuable suggestions.

This work was financially supported by intramural grants and by grants from the Deutsche Forschungsgemeinschaft (SFB1064/TP A13 and SFB-TR36/TP A04), Deutsche Krebshilfe (107277 and 109661), and National Cancer Institute (CA70723) and a personal grant to T.T. from Deutscher Akademischer Austauschdienst (DAAD) (Studienstipendien für ausländische Graduierte aller wissenschaftlichen Fächer).

## REFERENCES

1. Ressing ME, van Gent M, Gram AM, Hooykaas MJ, Piersma SJ, Wiertz EJ. 2015. Immune evasion by Epstein-Barr virus. Curr Top Microbiol Immunol 391:355–381. https://doi.org/10.1007/978-3-319-22834-1_12.
2. Bartel DP. 2009. MicroRNAs: target recognition and regulatory functions. Cell 136:215–233. https://doi.org/10.1016/j.cell.2009.01.002.
3. Mehta A, Baltimore D. 2016. MicroRNAs as regulatory elements in immune system logic. Nat Rev Immunol 16:279–294. https://doi.org/10.1038/nri.2016.40.
4. Pfeffer S, Sewer A, Lagos-Quintana M, Sheridan R, Sander C, Grasser FA, van Dyk LF, Ho CK, Shuman S, Chien M, Russo JJ, Ju J, Randall G, Lindenbach BD, Rice CM, Simon V, Ho DD, Zavolan M, Tuschl T. 2005. Identification of microRNAs of the herpesvirus family. Nat Methods 2:269–276. https://doi.org/10.1038/nmeth746.
5. Pfeffer S, Zavolan M, Grasser FA, Chien M, Russo JJ, Ju J, John B, Enright AJ, Marks D, Sander C, Tuschl T. 2004. Identification of virus-encoded microRNAs. Science 304:734–736. https://doi.org/10.1126/science.1096781.
6. Qiu J, Cosmopoulos K, Pegtel M, Hopmans E, Murray P, Middeldorp J, Shapiro M, Thorley-Lawson DA. 2011. A novel persistence associated EBV miRNA expression profile is disrupted in neoplasia. PLoS Pathog 7:e1002193. https://doi.org/10.1371/journal.ppat.1002193.
7. Seto E, Moosmann A, Gromminger S, Walz N, Grundhoff A, Hammerschmidt W. 2010. Micro RNAs of Epstein-Barr virus promote cell cycle progression and prevent apoptosis of primary human B cells. PLoS Pathog 6:e1001063. https://doi.org/10.1371/journal.ppat.1001063.
8. Choy EY, Siu KL, Kok KH, Lung RW, Tsang CM, To KF, Kwong DL, Tsao SW, Jin DY. 2008. An Epstein-Barr virus-encoded microRNA targets PUMA to promote host cell survival. J Exp Med 205:2551–2560. https://doi.org/10.1084/jem.20072581.
9. Feederle R, Linnstaedt SD, Bannert H, Lips H, Bencun M, Cullen BR, Delecluse HJ. 2011. A viral microRNA cluster strongly potentiates the transforming properties of a human herpesvirus. PLoS Pathog 7:e1001294. https://doi.org/10.1371/journal.ppat.1001294.
10. Vereide DT, Seto E, Chiu YF, Hayes M, Tagawa T, Grundhoff A, Hammerschmidt W, Sugden B. 2014. Epstein-Barr virus maintains lymphomas via its miRNAs. Oncogene 33:1258–1264. https://doi.org/10.1038/onc.2013.71.
11. Ramalingam D, Kieffer-Kwon P, Ziegelbauer JM. 2012. Emerging themes from EBV and KSHV microRNA targets. Viruses 4:1687–1710. https://doi.org/10.3390/v4091687.
12. Cullen BR. 2013. MicroRNAs as mediators of viral evasion of the immune system. Nat Immunol 14:205–210. https://doi.org/10.1038/ni.2537.
13. Walz N, Christalla T, Tessmer U, Grundhoff A. 2010. A global analysis of evolutionary conservation among known and predicted gammaherpesvirus microRNAs. J Virol 84:716–728. https://doi.org/10.1128/JVI.01302-09.
14. Nachmani D, Stern-Ginossar N, Sarid R, Mandelboim O. 2009. Diverse herpesvirus microRNAs target the stress-induced immune ligand MICB to escape recognition by natural killer cells. Cell Host Microbe 5:376–385. https://doi.org/10.1016/j.chom.2009.03.003.
15. Gottwein E, Corcoran DL, Mukherjee N, Skalsky RL, Hafner M, Nusbaum JD, Shamulailatpam P, Love CL, Dave SS, Tuschl T, Ohler U, Cullen BR. 2011. Viral microRNA targetome of KSHV-infected primary effusion lymphoma cell lines. Cell Host Microbe 10:515–526. https://doi.org/10.1016/j.chom.2011.09.012.
16. Hooykaas MJG, van Gent M, Soppe JA, Kruse E, Boer IGJ, van Leenen D,

Groot Koerkamp MJA, Holstege FCP, Ressing ME, Wiertz EJHJ, Lebbink RJ. 2017. EBV microRNA BART16 suppresses type I IFN signaling. J Immunol 198:4062–4073. https://doi.org/10.4049/jimmunol.1501605.
17. Ramalingam D, Ziegelbauer JM. 2017. Viral microRNAs target a gene network, inhibit STAT activation, and suppress interferon responses. Sci Rep 7:40813. https://doi.org/10.1038/srep40813.
18. Bauer S, Groh V, Wu J, Steinle A, Phillips JH, Lanier LL, Spies T. 1999. Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. Science 285:727–729. https://doi.org/10.1126/science.285.5428.727.
19. Stern-Ginossar N, Elefant N, Zimmermann A, Wolf DG, Saleh N, Biton M, Horwitz E, Prokocimer Z, Prichard M, Hahn G, Goldman-Wohl D, Greenfield C, Yagel S, Hengel H, Altuvia Y, Margalit H, Mandelboim O. 2007. Host immune system gene targeting by a viral miRNA. Science 317:376–381. https://doi.org/10.1126/science.1140956.
20. Song Y, Li X, Zeng Z, Li Q, Gong Z, Liao Q, Li X, Chen P, Xiang B, Zhang W, Xiong F, Zhou Y, Zhou M, Ma J, Li Y, Chen X, Li G, Xiong W. 2016. Epstein-Barr virus encoded miR-BART11 promotes inflammation-induced carcinogenesis by targeting FOXP1. Oncotarget 7:36783–36799. https://doi.org/10.18632/oncotarget.9170.
21. Qin Z, Kearney P, Plaisance K, Parsons CH. 2010. Pivotal advance: Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded microRNA specifically induce IL-6 and IL-10 secretion by macrophages and monocytes. J Leukoc Biol 87:25–34. https://doi.org/10.1189/jlb.0409251.
22. Quinn SR, O'Neill LA. 2011. A trio of microRNAs that control Toll-like receptor signalling. Int Immunol 23:421–425. https://doi.org/10.1093/intimm/dxr034.
23. Motsch N, Pfuhl T, Mrazek J, Barth S, Grässer FA. 2007. Epstein-Barr virus-encoded latent membrane protein 1 (LMP1) induces the expression of the cellular microRNA miR-146a. RNA Biol 4:131–137. https://doi.org/10.4161/rna.4.3.5206.
24. Lo AK, To KF, Lo KW, Lung RW, Hui JW, Liao G, Hayward SD. 2007. Modulation of LMP1 protein expression by EBV-encoded microRNAs. Proc Natl Acad Sci U S A 104:16164–16169. https://doi.org/10.1073/pnas.0702896104.
25. Albanese M, Tagawa T, Bouvet M, Maliqi L, Lutter D, Hoser J, Hastreiter M, Hayes M, Sugden B, Martin L, Moosmann A, Hammerschmidt W. 2016. Epstein-Barr virus microRNAs reduce immune surveillance by virus-specific $CD8^+$ T cells. Proc Natl Acad Sci U S A 113:E6467–E6475. https://doi.org/10.1073/pnas.1605884113.
26. Sullivan CS, Grundhoff AT, Tevethia S, Pipas JM, Ganem D. 2005. SV40-encoded microRNAs regulate viral gene expression and reduce susceptibility to cytotoxic T cells. Nature 435:682–686. https://doi.org/10.1038/nature03576.
27. Tagawa T, Albanese M, Bouvet M, Moosmann A, Mautner J, Heissmeyer V, Zielinski C, Lutter D, Hoser J, Hastreiter M, Hayes M, Sugden B, Hammerschmidt W. 2016. Epstein-Barr viral miRNAs inhibit antiviral $CD4^+$ T cell responses targeting IL-12 and peptide processing. J Exp Med 213:2065–2080. https://doi.org/10.1084/jem.20160248.
28. Lung RW, Tong JH, Sung YM, Leung PS, Ng DC, Chau SL, Chan AW, Ng EK, Lo KW, To KF. 2009. Modulation of LMP2A expression by a newly identified Epstein-Barr virus-encoded microRNA miR-BART22. Neoplasia 11:1174–1184. https://doi.org/10.1593/neo.09888.
29. Fåhraeus R. 2005. Do peptides control their own birth and death? Nat Rev Mol Cell Biol 6:263–267. https://doi.org/10.1038/nrm1590.
30. Kim S, Lee S, Shin J, Kim Y, Evnouchidou I, Kim D, Kim YK, Kim YE, Ahn JH, Riddell SR, Stratikos E, Kim VN, Ahn K. 2011. Human cytomegalovirus microRNA miR-US4-1 inhibits CD8(+) T cell responses by targeting the aminopeptidase ERAP1. Nat Immunol 12:984–991. https://doi.org/10.1038/ni.2097.
31. Stark TJ, Arnold JD, Spector DH, Yeo GW. 2012. High-resolution profiling and analysis of viral and host small RNAs during human cytomegalovirus infection. J Virol 86:226–235. https://doi.org/10.1128/JVI.05903-11.
32. Xia T, O'Hara A, Araujo I, Barreto J, Carvalho E, Sapucaia JB, Ramos JC, Luz E, Pedroso C, Manrique M, Toomey NL, Brites C, Dittmer DP, Harrington WJJ. 2008. EBV microRNAs in primary lymphomas and targeting of CXCL-11 by EBV-mir-BHRF1-3. Cancer Res 68:1436–1442. https://doi.org/10.1158/0008-5472.CAN-07-5126.
33. Jochum S, Moosmann A, Lang S, Hammerschmidt W, Zeidler R. 2012. The EBV immunoevasins vIL-10 and BNLF2a protect newly infected B cells from immune recognition and elimination. PLoS Pathog 8:e1002704. https://doi.org/10.1371/journal.ppat.1002704.
34. Zhang G, Zong J, Lin S, Verhoeven RJ, Tong S, Chen Y, Ji M, Cheng W, Tsao SW, Lung M, Pan J, Chen H. 2015. Circulating Epstein-Barr virus microRNAs miR-BART7 and miR-BART13 as biomarkers for nasopharyngeal carcinoma diagnosis and treatment. Int J Cancer 136:E301-12. https://doi.org/10.1002/ijc.29206.
35. Pegtel DM, Cosmopoulos K, Thorley-Lawson DA, van Eijndhoven MA, Hopmans ES, Lindenberg JL, de Gruijl TD, Wurdinger T, Middeldorp JM. 2010. Functional delivery of viral miRNAs via exosomes. Proc Natl Acad Sci U S A 107:6328–6333. https://doi.org/10.1073/pnas.0914843107.
36. Gallo A, Vella S, Miele M, Timoneri F, Di Bella M, Bosi S, Sciveres M, Conaldi PG. 2017. Global profiling of viral and cellular non-coding RNAs in Epstein-Barr virus-induced lymphoblastoid cell lines and released exosome cargos. Cancer Lett 388:334–343. https://doi.org/10.1016/j.canlet.2016.12.003.
37. Baglio SR, van Eijndhoven MA, Koppers-Lalic D, Berenguer J, Lougheed SM, Gibbs S, Léveillé N, Rinkel RN, Hopmans ES, Swaminathan S, Verkuijlen SA, Scheffer GL, van Kuppeveld FJ, de Gruijl TD, Bultink IE, Jordanova ES, Hackenberg M, Piersma SR, Knol JC, Voskuyl AE, Wurdinger T, Jiménez CR, Middeldorp JM, Pegtel DM. 2016. Sensing of latent EBV infection through exosomal transfer of 5′pppRNA. Proc Natl Acad Sci U S A 113:E587–E596. https://doi.org/10.1073/pnas.1518130113.
38. Nanbo A, Kawanishi E, Yoshida R, Yoshiyama H. 2013. Exosomes derived from Epstein-Barr virus-infected cells are internalized via caveola-dependent endocytosis and promote phenotypic modulation in target cells. J Virol 87:10334–10347. https://doi.org/10.1128/JVI.01310-13.
39. Haneklaus M, Gerlic M, Kurowska-Stolarska M, Rainey AA, Pich D, McInnes IB, Hammerschmidt W, O'Neill LA, Masters SL. 2012. Cutting edge: miR-223 and EBV miR-BART15 regulate the NLRP3 inflammasome and IL-1beta production. J Immunol 189:3795–3799. https://doi.org/10.4049/jimmunol.1200312.
40. Chevillet JR, Kang Q, Ruf IK, Briggs HA, Vojtech LN, Hughes SM, Cheng HH, Arroyo JD, Meredith EK, Gallichotte EN, Pogosova-Agadjanyan EL, Morrissey C, Stirewalt DL, Hladik F, Yu EY, Higano CS, Tewari M. 2014. Quantitative and stoichiometric analysis of the microRNA content of exosomes. Proc Natl Acad Sci U S A 111:14888–14893. https://doi.org/10.1073/pnas.1408301111.
41. Jochum S, Ruiss R, Moosmann A, Hammerschmidt W, Zeidler R. 2012. RNAs in Epstein-Barr virions control early steps of infection. Proc Natl Acad Sci U S A 109:E1396-404. https://doi.org/10.1073/pnas.1115906109.
42. Skalsky RL, Cullen BR. 2015. EBV noncoding RNAs. Curr Top Microbiol Immunol 391:181–217. https://doi.org/10.1007/978-3-319-22834-1_6.
43. Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, van der Meer AJ, Patick AK, Chen A, Zhou Y, Persson R, King BD, Kauppinen S, Levin AA, Hodges MR. 2013. Treatment of HCV infection by targeting microRNA. N Engl J Med 368:1685–1694. https://doi.org/10.1056/NEJMoa1209026.
44. Verhoeven RJ, Tong S, Zhang G, Zong J, Chen Y, Jin DY, Chen MR, Pan J, Chen H. 2016. NF-κB signaling regulates expression of Epstein-Barr virus BART microRNAs and long noncoding RNAs in nasopharyngeal carcinoma. J Virol 90:6475–6488. https://doi.org/10.1128/JVI.00613-16.