Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
CHAPTER 10

Targeting histone epigenetics to control viral infections

Zeina Nehme\textsuperscript{a,b}, Sébastien Pasquereau\textsuperscript{a}, and Georges Herbein\textsuperscript{a,c}

\textsuperscript{a}Department Pathogens & Inflammation-EPILAB, UPRES EA4266, University of Franche-Comté, University of Bourgogne Franche-Comté, Besançon, France
\textsuperscript{b}Lebanese University, Beirut, Lebanon
\textsuperscript{c}Department of Virology, CHRU Besançon, Besançon, France

10.1 Chronic viral infections

10.1.1 Human immunodeficiency virus (HIV)

HIV-1 infection shifted from being a fatal illness to a chronic infection with the introduction and enhancement of combined antiretroviral therapy (cART). However, HIV-1 infection remains an incurable disease due to the presence of latently infected cells, in which a provirus is silenced through epigenetic regulation.\textsuperscript{7,8} This transcriptional silencing is reversible and under the control of the host chromatin-modifying enzymes, leading to viral rebound and a persistence of the infection.\textsuperscript{9} Histone modifications are a well-known component of HIV-1 latency regulation, as these impact the HIV-1 long terminal repeats (LTR) accessibility to transcription factors. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are responsible for the acetylation state of histones, while histone methyltransferases (HMT) are responsible for the methylation state. HATs are generally responsible for the activation of viral gene expression, while HDACs and HMTs are associated with the silencing of viral gene expression, thereby inducing latency.\textsuperscript{10} Cellular host factors recruit HDACs to HIV-1 5’LTR, resulting in the repression of the HIV-1-associated nucleosome nuc-1.\textsuperscript{11} HMTs also induce the silencing of proviral DNA by changing the methylation state of histone H3, resulting in the condensation of nuc-1.\textsuperscript{11} Therapeutic approaches to eradicate the latent provirus can be separated into two opposite dogmas: the shock and kill strategy, which aims at reactivating the latent virus to be able to kill infected cells; and the block and lock strategy, a new approach that aims at blocking the viral genome into a nonreversible latency (Fig. 10.1).\textsuperscript{8,11,12} In the block and lock strategy, the histone modifications associated with latency are made stable by preventing further modifications to the methylation or acetylation state of the histones and blocking the latency reversing agents and LTR activators (Fig. 10.2).\textsuperscript{8} In the shock and kill strategy, combined antiretroviral therapy (cART), in charge of the killing, is associated with latency reversing agents (LRAs), which are mainly HDAC and HMT inhibitors.\textsuperscript{11,13} HDAC inhibitors were first tested in cancer research,
Fig. 10.1 Targeting histone acetylation in the management of chronic viral infections (HIV, HCMV, RSV), virus-induced cancers (EBV, HCV, HTLV, HPV, HBV, KSHV), and epidemic/emerging viruses (WNV, BDV).
Fig. 10.2 Targeting histone methylation in the management of chronic viral infections (HIV, HSV, HCMV, RSV), virus-induced cancers (EBV, KHSV), and epidemic/emerging viruses (IAV, ZIKV, SARS-CoV, MERS-CoV).
where they showed a low toxic profile and an absence of T cell activation.\textsuperscript{14} Several FDA-approved HDAC inhibitors, including vironostat or valproic acid, were shown to reactivate HIV-1 from latently infected cells (summarized in Table 10.1). Trials of HDACs-driven reactivation conducted in patients under cART have been reported; however, the efficiency of LRAs in aviremic cART-treated patients was shown to be insufficient to induce a viral outgrowth.\textsuperscript{44} Interestingly, treatment with HDAC inhibitor romidepsin was reported to prevent de novo infection of CD4+ T cells.\textsuperscript{45,46} More recent approaches for clearing latently infected cells of HIV included the use of HDAC inhibitor SAHA in association with a global T-cell activator, resulting in a synergistic effect on purging the proviruses from the cells.\textsuperscript{47} HMT inhibitors also showed promising results as LRAs. These inhibitors, especially the ones targeting EZH2 and G9a, were shown to induce an HIV-1 viral production when associated with HDAC inhibitors, by altering the histone H3 methylation pattern at the 5'LTR.\textsuperscript{48–52} Tables 10.1 and 10.2 summarize the functional outcomes of histone acetylation and methylation manipulation, respectively, in the HIV context, as well as for other viruses.

### 10.1.2 Herpes simplex virus (HSV)

Belonging to the Herpesviridae family, Herpes simplex virus (HSV) is a double-stranded DNA virus with a structurally complex 152-kbp genome.\textsuperscript{64} The global estimates identify 3.709 billion people or 67% of the total population as being infected by this highly infectious pathogen. As it is generally limited to oral and labial mucosal lesions in immunocompetent host, HSV-1 infection is occasionally recognized as a cause of sporadic encephalitis, stromal keratitis, and corneal scarring in children and adults, in addition to hepatitis and pneumonia in immunocompromised patients.\textsuperscript{65,66} The HSV life cycle begins with a productive or lytic infection of mucosal epithelial cells, from where the newly produced virions spread and enter the sensory neuron axons. Retrograde microtubule-associated molecular motors ensure the delivery of the viral capsid carrying the viral genome into the nucleus of the neurons of sensory ganglia. Once released, viral DNA circulates and steadily persists in an episomal form, along with repression of viral lytic genes expression, a state known as latency.\textsuperscript{67} Occasionally, and in response to various stimuli, the latent virus could be reactivated where lytic infection and production of infectious particles are resumed.\textsuperscript{68} It has been hypothesized that the establishment of latency or even the lytic-latent switch is closely associated with histone modifications, suggesting a potential to manipulate those changes to control HSV infection.\textsuperscript{69} In this context, LSD1 or KDM1A, a lysine-specific histone demethylase, has gained special attention. Due to its recruitment with the histone H3K4 methyltransferase Set1/MLL and the cellular transcriptional coactivator HCF-1, the repressive H3K9 methylation marks are replaced by activating H3K4 methylation marks, resulting in promotion of lytic
| Target class | Target | Inhibitor | Virus studied | Functional outcome |
|--------------|--------|----------|--------------|--------------------|
| HDAC         | Pan-HDAC | Valproic acid (VPA) | HCMV | Increase in HCMV IE antigen 1 and late antigen expression 15 |
|              |        |          |              | HBV | Increase in viral transcripts and secreted particles 16 |
|              |        |          |              | HTLV-1 | Activation and collapse of latent viral reservoir in vitro, ex vivo, and in HAM/TSP patients 17 |
|              |        |          |              |     | Enhancement and prolongation of Tax-mRNA expression 18 |
|              |        |          |              |     | Increase in the number of Tax-expressing provirus-positive cells 19 |
|              | Pan-HDAC | Trichostatin A (TSA) | DENV | Reduction in the secretion of inflammatory cytokines 20 |
|              |        |          |              | WNV | Inhibition of complete viral yield 21 |
|              |        |          |              | HCMV | Acceleration of viral replication in human foreskin fibroblast cells 22 |
|              |        |          |              |     | Reactivation of the major immediate-early regulatory region (MIERR) in human embryonal NTera2 carcinoma (NT2) cells 23 |
|              |        |          |              | RSV | Viral replication restriction 24 |
|              |        |          |              | HBV | Increase in viral transcripts and secreted particles 16 |
|              |        |          |              | EBV | Activation of EBV lytic cycle gene expression in cellosaurus cell line HH514-16 but not in marmoset B-cell line B95-8 25 |
|              |        |          |              | HPV | Induction of intrinsic type II apoptosis in HPV-16 E7-positive cervical carcinoma cells 26 |
|              |        |          |              |     | Block in G1 to S transition and subsequent apoptosis induction in HPV-18-positive cervical carcinoma cells 27 |
|              | Pan-HDAC | Vorinistat/suberanilohydroxamic acid (SAHA) | JCV | Stimulation of early and late transcription 28 |
|              |        |          |              | HIV | Reactivation of HIV-1 in cells derived from infected patients 11 |
|              |        |          |              |     | Increase in cell-associated unspliced HIV-1 RNA levels and in global acetylation 11 |
|              |        |          |              |     | Purging of HIV-1 proviruses in HIV-1 latently infected cells 12 |
|              |        |          |              | RSV | Restriction of viral replication 24 |
### Table 10.1 Functional outcomes of histone acetylation regulation in viral infections—cont’d

| Target class | Target | Inhibitor | Virus studied | Functional outcome |
|--------------|--------|-----------|---------------|--------------------|
|              |        |           |               | HBV                |
|              |        | Sodium butyrate | EBV  | Stimulation of HBV replication$^{29}$ |
| HBV          |        |           |               | HCV                |
|              |        | Sodium butyrate | EBV  | Stimulation of HBV replication$^{29}$ |
| HCV          |        |           |               | Suppression of HCV replication$^{30}$ |
|              |        |           |               | Suppression of HCV replication in an in vivo model of immunocompromised humanized transgenic mice$^{31}$ |
| HPV          |        |           |               | Abrogation of viral DNA amplification and host DNA replication plus a reduction in the E7-induced DNA damage response and E6- and E7-induced destabilization of the major tumor suppressor p53 and pRB proteins, respectively$^{32}$ |
|              |        |           |               | Induction of intrinsic type II apoptosis in HPV-16 E7-positive cervical carcinoma cells$^{26}$ |
| HTLV-1       |        |           |               | Inhibition of proliferation in HTLV-1-infected T cells and fresh clinically isolated ATL cells and induction of cell cycle arrest at the G2/M phase and apoptosis in infected cells$^{33}$ |
|              |        |           |               | Counteracting the damaging effects of BDV-1 on synaptic plasticity$^{34}$ |
| BDV          |        |           |               | Pan-HDAC Sodium butyrate | EBV | Activation of EBV lytic cycle gene expression in the cellosaurus cell line but not in marmoset$^{25}$ |
|              |        |           |               | HPV Block in G1 to S transition plus apoptosis indication in HPV-18-positive cervical carcinoma cells$^{27}$ |
|              |        |           |               | JCV Stimulation of early and late transcription$^{28}$ |
|              |        |           |               | HDAC1/2/3 CI994I   | HCV | Suppression of HCV replication$^{31}$ |
|              |        |           |               | HDAC3 RGFP966      | HCV | Suppression of HCV replication$^{31}$ |
|              |        |           |               | HDAC6 Tubastatin A | HCV | Establishment of an antiviral activity in human hepatocytes$^{36}$ |
|              |        |           |               | HDAC1,2,3 Depsipeptide | HCV | Establishment of an antiviral activity in human hepatocytes$^{36}$ |
|              |        |           |               | HTLV-1            | HCV | Establishment of an antiviral activity in human hepatocytes$^{36}$ |
| Combination                                      | TSA + DZNep          | EBV                               | Induction of BZLF1 transcription$^{38}$ |
|-------------------------------------------------|----------------------|-----------------------------------|-----------------------------------------|
| HDAC inhibitor + HMT inhibitor                   |                      |                                   |                                         |
| HDAC inhibitor + proteasome inhibitor            | SAHA + bortezomib    | KSHV                              | Eradication of KSHV-infected primary effusion lymphoma cells$^{39}$ |
| HDAC inhibitor + proteasome inhibitor            | TSA or vorinostat + bortezomib | HPV                              | Induction of a caspase-mediated apoptosis in cervical cancer cells$^{40}$ |
| HDAC inhibitor + protein kinase C inhibitor      | Sodium butyrate + UCN-01 | HPV                              | Enhancement in intrinsic apoptotic pathways in HPV-positive human cervical carcinoma cells plus inhibition of tumor growth in xenografted nude mice$^{41}$ |
| HDAC inhibitor + DNA and RNA polymerase inhibitor| SAHA + mithramycin A | MCV                              | Reinduction of the expression of MHC class I chain-related protein (MIC) in vitro and in vivo, rendering Merkel cell carcinoma (MCC) cells more sensitive to lysis by cytotoxic lymphocytes$^{42}$ |
| HDAC inhibitor + adenosine analogue inhibitor    | SAHA + NITD008       | WNV                              | Decrease in the mRNA levels of inflammatory cytokines and improved disease outcome in C57BL/6 mice$^{43}$ |
Table 10.2 Functional outcomes of histone methylation regulation in viral infections.

| Target class | Target      | Inhibitor | Virus studied | Functional outcome |
|--------------|-------------|-----------|---------------|--------------------|
| HAT          | Gcn5P       | CPTH2     | BKV           | Decrease in the major capsid protein VP1 expression<sup>53</sup> |
| HMT          | Suv39H      | Chaetocin | EBV           | Transactivation of BZLF1 gene in B95-8 cells but not in Akata or Raji cells<sup>54</sup> |
|              | G9a         | BIX-01294 | HIV           | Reversal of HIV-1 latency in model cell lines and cells derived from patients<sup>11</sup> |
|              | EZH2        | GSK126    | HIV           | Reversal of HIV-1 latency in model cell lines and cells derived from patients<sup>11</sup> |
|              |             | GSK343    | HSV-1         | Reduction in HSV gene expression and lytic infection in vitro and in vivo and suppression of viral reactivation in a ganglion explant model<sup>55</sup> |
|              |             |           | ZIKV          | Suppression of infection<sup>55</sup> |
|              |             |           | HSV-1         | Reduction in HSV gene expression and lytic infection in vitro and in vivo and suppression of viral reactivation in a ganglion explant model<sup>55</sup> |
|              |             |           | HCMV          | Stimulation of significant increases in the lytic RNA transcript expression<sup>56</sup> |
|              | UNC1999     | HSV-1     | HIV           | Reversal of HIV-1 latency in model cell lines and cells derived from patients<sup>11</sup> |
|              | DZNep       | HIV       | HCMV          | Induction of activation of the lytic transcription program in two cellular models of HCMV quiescence<sup>56</sup> |
|              | DOT1L       | EPZ-5676  | HPV           | Antiproliferative characteristics in HPV-positive oropharyngeal squamous cell carcinomas<sup>57</sup> |
|              |             | IVA       |               | Increase in viral replication<sup>58</sup> |
### Table 10.2 Functional outcomes of histone methylation regulation in viral infections—cont’d

| Target class | Target | Inhibitor | Virus studied | Functional outcome |
|--------------|--------|-----------|---------------|--------------------|
| HDM          | KDM1A  | OG-L002   | HSV-1         | Inhibition of HSV lytic infection in vivo and blockage of reactivation from latency in a mouse ganglion explant model<sup>59</sup> |
|              |        | TCP       | HCMV/HSV-1    | Repression of the expression of HCMV IE genes<sup>59</sup> |
|              | KDM4   | DMOG      | HCMV/HSV-1    | Repression of the expression of HCMV IE genes<sup>61</sup> |
|              |        | 2,4-PDCA  | HCMV          | Block of the initiation of viral productive infection and reactivation in the sensory ganglia of latently infected mice<sup>61</sup> |
|              | KDM5B  | ML324     | HSV-1         | Decrease in the expression of the UL37, UL72, and US3 HCMV genes<sup>61</sup> |
|              | Bim1   | PTC-209   | RSV           | Seventy-five-fold more efficiency in suppressing infection than DMOG<sup>61</sup> |
|              |        | TCP + acyclovir | HSV-1       | Increase in survival of infected mouse<sup>60</sup> |
| Polycomb repressive complex 1 | | | | |
| Combination | HDM inhibitor + DNA polymerase inhibitor | | | |

<sup>59</sup> Reference: [59]

<sup>60</sup> Reference: [60]

<sup>61</sup> Reference: [61]

<sup>62</sup> Reference: [62]

<sup>63</sup> Reference: [63]
infection or reactivation from latency.\textsuperscript{70} It has been shown that the use of OG-L002, a highly specific and potent LSD1 inhibitor, significantly inhibited HSV immediate-early (IE) gene expression while accumulating repressive chromatin assembly on viral IE gene promoter in vitro, repressed HSV lytic infection in vivo, and blocked HSV reactivation from latency in a mouse ganglion explant model.\textsuperscript{59} Another LSD1 inhibitor, tranylcypromine (TCP), suppressed lytic infection in a mouse model of neonatal infection and in a rabbit eye model of herpetic keratitis. In addition, TCP reduced viral reactivation and shedding, as well as lesion recurrence in a guinea pig vaginal model. Interestingly, combining TCP with the conventional antiviral acyclovir increased survival of infected mice compared to treatment with either compound individually.\textsuperscript{60} As LSD1 removes mono- and dimethylation marks,\textsuperscript{71} the activity of another demethylase, JMJD2, is indispensable to remove trimethylation.\textsuperscript{72} It has been shown that the use of dimethylxalylglycine (DMOG), a JMJD2 inhibitor, blocked both the initiation of viral productive infection and reactivation, detected through a decreased IE gene expression along with an increase in the levels of the repressive H3K9-me3 marks on IE gene promoters in the sensory ganglia of latently infected mice. Another JMJD2 inhibitor denoted as ML324 was approximately 75-fold more efficient than DMOG in suppressing infection.\textsuperscript{61} Not limited to demethylase, the histone H3K27 methyltransferase enhancer of zeste homolog 1 and 2 (EZH1 and EZH2, respectively) inhibitors GSK126, GSK343, and UNC1999 surprisingly reduced HSV gene expression and lytic infection in vitro and in vivo and suppressed viral reactivation in a ganglion explant model, in contrast to the expected suppressive role of EZH2/1, and thus the predictable activation following its inhibition (Fig. 10.2). This suppression of viral genome is due possibly to the induction of a cellular antiviral state via IFN/immune signaling-related pathways, which suggests the short-term use of such inhibitors as immune enhancers or general potential antivirals to boost viral clearance.\textsuperscript{55} However, it has been shown that HSV is able to induce reactivation in latency even in the presence of repressive lysine methylation marks in a primary mouse sympathetic neurons model. Stress-induced activation of c-Jun N-terminal kinase (JNK) signaling pathway results in a histone methyl/phospho switch on HSV lytic promoters, thereby increasing phosphorylation on histone H3 while maintaining the repressive methylation marks on nucleosome-associated viral lytic gene promoters, neglecting the activating role of LSD1 and UTX/JMJD3 during phase I of reactivation.\textsuperscript{73} This suggests that additional histone modifications, for instance, phosphorylation, can correspondingly modulate repression. It is critical to determine the exact interaction between various epigenetic players and cellular factors during lytic and latent infection, in addition to reactivation, as this can pave the way toward the introduction of novel potential antiviral agents that could eradicate or at least control HSV infection and lessen its global burden.
Another member of the Herpesviridae family is the human cytomegalovirus or, alternatively, the human herpes virus 5 (HHV-5). Although HCMV affects 40%-99% of the population, its real burden is emphasized in the context of immunocompromised patient, including mainly transplant recipients and HIV patients where HCMV infection is linked to pneumonitis, colitis, retinitis, hepatitis, transplant rejection, and myelosuppression. Furthermore, HCMV infection is correlated with hepatosplenomegaly, cognitive impairment, microcephaly, mild-to-severe sensorineural hearing loss, developmental delay, and cerebral palsy in the context of congenital infection. Thus novel approaches to control HCMV infection are exceedingly important as no vaccine is currently available and the long-term use of the available antivirals is limited due to the emergence of resistance and toxicity. Added to this is the fact that those antivirals block the viral DNA replication, not controlling thus the early stages of the infection during which the expression of the IE and early (E) HCMV genes could induce tissue damage and raise the risk of graft rejection along with viral shedding and transmission. Most importantly, the persistence of the virus in a state of cellular latency following primary infection, coupled with potential occasional reactivation events, establishes an important barrier against eradicating the virus. However, recent advances in understanding the molecular basis of HCMV pathogenesis and life cycle have offered many insights to control and possibly eliminate HCMV infection. Indeed, the genome complexity and the dynamic virus-host interaction offer a rich molecular podium, in which a multitude of diverse players could be manipulated to modulate and control the lytic and latent patterns of infection. In this regard and in parallel to HSV infection, the LSD1 inhibitors OG-L002 or TCP significantly repressed the expression of HCMV IE genes, and the JMJ2 inhibitor DMOG decreased the expression of the UL37, UL72, and US3 HCMV genes with a more potent inhibition noted with the use of ML324. Another methyltransferase, the disruptor of telomeric silencing 1-like (DOT1L), responsible for mono-, di-, or trimethylation of lysine 79 of histone H3, is upregulated upon lytic infection with concurrent spike in H3K79me2. Interestingly, DOT1L knockdown ensured a 10-fold growth defect resulting in decreased virus production compared with controls (Fig. 10.2). While this approach blocks the virus during the early stages of the lytic infection, or locks it in a super latency state preventing its reactivation, another stratagem is activating and purging the existent latent reservoir and subsequently eradicating the infection. This corresponds to the “shock and kill” approach discussed in the preceding section in the perspective of HIV infection. In this regard, the polycomb repressive complex 2 (PRC2) appears to play a pivotal role in the establishment and maintenance of HCMV latency partly due to its catalytic subunit known as EZH2, the latter responsible for the trimethylation of the lysine 27 residues of histone H3 (H3K27me3). The use of DZnep, a potent EZH2 inhibitor, induced a significant activation of the lytic
transcription program in two cellular models of HCMV quiescence. Moreover, inhibition of PRC2 by GSK343 stimulated a significant increase in the lytic RNA transcripts expression.\textsuperscript{56} In contrast to the repressive function during latency and independently from the catalytic function of PRC1 and PRC2, a recent study showed that following lytic infection, all major PRC1 and PRC2 components, RING1B, BMI1 and EZH2, EED, SUZ12, respectively, were upregulated at the transcript and protein level where they endorsed a proviral state that promoted efficient HCMV DNA replication. In line with this, the use of diverse PRC1/2 inhibitors showed that only substances negatively affecting the complex stability, namely, DZNep, 484 WDL, and PTC-209, had the capacity to compromise HCMV genome synthesis, suggesting thus a noncanonical function of PRCs during lytic infection and demonstrating a potential novel antiviral strategy as those substances inhibited viral spread to an extent equivalent to ganciclovir over several HCMV replication cycles.\textsuperscript{86} On the other hand, a dynamic acetylation-deacetylation pattern of HCMV chromatin is noted during various stages of the infectious cycle.\textsuperscript{87} In fact, histone deacetylases (HDACs) are known to play a role in the repression of viral replication.\textsuperscript{88} The use of the deacetylase inhibitor trichostatin A (TSA) significantly accelerated viral replication as evidenced by a 10-fold higher production of infectious viral particles upon TSA treatment in human foreskin fibroblast cells (HFF).\textsuperscript{22} Likewise, TSA induced a 19.6-fold increase in the amount of IE1 RNAs, inducing thus the reactivation of major immediate-early regulatory region (MIERR) in human embryonal NTera2 carcinoma (NT2) cells.\textsuperscript{23} In addition, valproic acid (VPA), another histone deacetylase inhibitor, resulted in a 4-fold increase in HCMV IE antigen 1 (IEA1) and late antigen (LA) expression and an approximate 8-fold increase of HCMV IEA1 and HCMV IEA2 mRNA levels (Fig. 10.1).\textsuperscript{15} Whether to suppress lytic infection and prevent reactivation or to activate the latent reservoir and eradicate it to establish a sterilizing cure, a better understanding of the molecular mechanisms involved in HCMV infection as well as further studies to determine the activity of those inhibitors in animal models as a proof-of-concept is highly needed.

10.1.4 Respiratory syncytial virus (RSV)

Respiratory syncytial virus (RSV), a negative-sense RNA virus belonging to the Paramyxoviridae family, is considered the most common cause of childhood acute lower respiratory infection (ALRI) and the third causative agent of childhood death from pneumonia after Streptococcus pneumonia and Haemophilus influenza type b infection.\textsuperscript{89,90} Not limited to children, this pathogen is increasingly identified as a cause of illness in elderly and high-risk adults.\textsuperscript{91} A first report establishing a correlation between HDAC activity and RSV infectivity demonstrated that inhibiting HDAC through TSA and SAHA restricted viral replication by upregulating the interferon-\(\alpha\) (IFN\(\alpha\))-related
signaling pathways. Furthermore, the RSV-induced proinflammatory cytokine release and oxidative stress-related molecule production were significantly inhibited in vitro and in a mouse model of RSV infection after treatment with HDAC inhibitors (Fig. 10.1). Apart from HDAC, histone methylation appears to play a role during RSV infection. Exposing mouse dendritic cells (DC) and human monocyte-derived DCs (MoDCs) to RSV upregulated the expression of Kdm5b/Jarid1b H3K4 demethylase, whereas treatment with 2,4-pyridinedicarboxylic acid (2,4-PDCA), a chemical histone-lysine demethylase inhibitor, resulted in an increased production of proinflammatory cytokines, including TNF and IL6, and decreased Th2 pathogenesis in vivo (Fig. 10.2). This suggests that epigenetic regulation is involved in modulating the immune response during RSV infection and stresses on considering those modification in developing new antiviral strategies.

10.2 Cancer-inducing viruses

In the past decades, the molecular mechanisms and genome instability induced by oncogenic viruses during the tumorigenic process has gained increased attention as pathogens contribute to 20% of cancers worldwide. In this regard, dysregulation of some epigenetic regulators could play a role in the initiation or progression of carcinogenesis during infection with oncogenic viruses, along with disruption of genetic and molecular mechanisms and homeostasis. Taking into account such reprogramming, those epigenetic factors could potentially be manipulated to prevent and/or treat oncogenic virus-induced malignancies.

10.2.1 Hepatitis B virus (HBV)

Hepatitis B virus (HBV) is small DNA virus responsible for acute and chronic liver infection, which could eventually evolve into cirrhosis and hepatocellular carcinoma (HCC). Despite the introduction of FDA-approved antiviral drugs exemplified mainly by nucleos(t)ide analogues and pegylated interferon-α and expanded immunization, the number of individuals with chronic HBV infection is estimated to be 240 million, with the emergence of some drug-resistant mutations. This is mainly due to the persistence of HBV in the hepatocyte nucleus in the form of an episomal nonintegrated covalently closed circular (ccc) DNA susceptible to epigenetic modifications. As with other viruses, this cccDNA could constitute an appealing therapeutic epigenetic target to achieve complete silencing, diminishing viral replication, viremia, and infectivity, or alternatively to eliminate it through reactivation and succeeding eradication. In line with the former strategy, SIRT3, a class III histone deacetylase, restricted cccDNA transcription and HBV replication in HBV-infected HepG2-NTCP cells and primary human
hepatocytes (PHH) cells. This was mediated through H3K9 deacetylation and increased recruitment of SUV39H1 to cccDNA along with decreased recruitment of SETD1A, resulting in a marked increase of H3K9me3 and a decrease of H3K4me3.99 In this setting, it is worth pointing toward the crucial role of the hepatitis B viral protein HBx. In fact, the HBx regulatory protein is recruited onto the cccDNA minichromosome, where it increases histone acetylation and H3K4me3, with a concomitant decrease in H3K9me3, resulting in transcriptional reactivation. Conversely, in the absence of HBx, transcriptional silencing, along with a decrease in histone 3 acetylation and H3K4me3 and an increase in H3K9me, is noted, with a major role of SETDB1 in mediating HBV repression.100,101 Recalling the presence of a composite network of various players that could affect cccDNA transcription and HBV regulation sheds light on the necessity of revealing the enzymatic activities and mechanisms modulating the cccDNA-bound histone dynamics to identify potential new targets. Diversely, the use of the HDAC inhibitors VPA and TSA both increased HBV transcripts and secreted viral particles.16 In addition, the potent HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) induced an increase in HBsAg, HBeAg, and HBV DNA content, indicating a stimulation of HBV replication (Fig. 10.1).29 Also, a clinical case report of HBV reactivation detected through seropositivity of HBcAb IgG and HBsAb was described following romipedsin treatment.102 It must be stated that as those HDAC inhibitors are used to treat some malignancies (for example romipedsin for treatment of peripheral T-cell lymphoma103 and SAHA for advanced primary cutaneous T-cell lymphoma104), caution should be exercised when using such agents in HBV-positive cancer patients. Attractively and beyond viral infection control, SAHA exhibited a potential to be well thought out as a chemopreventive agent for high-risk chronic HBV patients who may develop HCC or whose HCC may recur after surgery. This is due to the ability of SAHA to attenuate the pre-S2 mutant large HBV surface antigen (LHBS)-induced JAB1-p27Kip1 interaction and recover normal cell cycle checkpoint in type II ground glass hepatocytes (GGHs) in vitro and in vivo.105 Extending this effect to other HDAC inhibitors and coupling this chemopreventive outcome to the potential epigenetic-controlled antiviral effect could be of high importance in the context of HBV infection.

10.2.2 Hepatitis C virus (HCV)

Being a member of the Flaviviridae family, Hepatitis C virus (HCV) is an enveloped single-stranded RNA virus affecting 177.5 million adults worldwide.106,107 Whereas acute infection is commonly asymptomatic and thus undetectable at the clinical level, only 15%-25% of the recently infected adults experience a spontaneous resolution.108 Indeed, the clearance or otherwise the persistence of an acute HCV infection diverges based on several factors such as age, gender, HCV genotype, viral coinfections,
imunologic responses, and many others. Given the complex interactions among various host, virologic, and immunologic factors, HCV infection can progress to a chronic state, leading possibly to cirrhosis, which can advance occasionally to HCC or liver failure. In addition, the persistence of HCV RNA is linked to extrahepatic complications, including cryoglobulinemia, type 2 diabetes mellitus, renal insufficiency, cardiovascular disorders, non-Hodgkin lymphoma, and others, that significantly impact the quality of life. Fortunately, while the previous interferon-based therapy and ribavirin were limited in terms of tolerability and success, the introduction of the HCV protease inhibitors/direct acting antiviral (DAA) therapies significantly ensured high efficacy and well-tolerated regimen with elevated cure rates. Despite this, high cost and complex treatment selection based on viral genotype and host factors such as liver decompensation and suboptimal renal excretion can limit access to treatment. In addition, although oral antiviral regimens cover all HVC genotypes, treatment of patients with the second most prevalent genotype 3 (GT 3), who are at a higher risk of developing HCC, is highly challenging as interferon-free treatment options are suboptimal. Given the epigenetic alterations associated with HCV infection and its link to HCC, epigenetic drugs could be used to target difficult-to-treat subgroups and special populations with a simplified treatment selection. The HDAC inhibitor SAHA, as well as TCA, inhibited HCV replication with no cellular toxicity. Interestingly, SAHA treatment induced osteopontin (OPN) upregulation, a vital cytokine for viral elimination via the induction of the Th1 immune response by stimulating histone H3 acetylation of the corresponding promoter. In addition, SAHA promoted apolipoprotein-A1 (Apo-A1) downregulation, a protein involved in HCV particle formation and maintenance of infectivity. However, another study pointed toward significant cytotoxicity at a low molar concentration of SAHA treatment despite its anti-HCV activity. Nevertheless, treatment with SAHA or the HDAC1/2/3 inhibitor CI994I or the HDAC3 inhibitor RGFP966 suppressed HCV replication in infected Huh7 cells, with no observed effect upon treatment with the HDAC8 inhibitor PCI-34051. Specifically, and consistent with the previously mentioned study, RGFP966 decreased the level of Apo-A1, which could suppress HCV assembly and secretion and increased the level of the liver-expressed antimicrobial peptide 1 (LEAP-1), which in turn could remit HCV infection and chronic liver injury. The role of SAHA and RGFP966 was confirmed in an in vivo model of immunocompromised humanized transgenic mice infected with HCV. Alternatively, Tubastatin A, a selective inhibitor of histone deacetylase 6, exhibited an antiviral activity in human hepatocytes, which also identifies HDAC6 as a potential promising cellular target in hepatitis C treatment (Fig. 10.1). Altogether, this indicates that the manipulation of histone deacetylases could be an effective strategy for managing HCV infection or HCV associated-diseases, with the imperative need to decipher the exact role of each HDAC and the effect of its subsequent inhibition.
10.2.3 Epstein–Barr virus (EBV)

Epstein–Barr virus (EBV) is a member of the family Herpesviridae, subfamily Gammaherpesvirinae. Also known as human herpesvirus 4 (HHV4), this DNA virus is considered a ubiquitous pathogen that affects approximately 90% of the world’s population. Nevertheless, EBV is correlated with a variety of tumors of both lymphoid and epithelial origin, including Burkitt’s lymphoma (BL), nasopharyngeal carcinoma (NPC), head and neck cancers, Hodgkin’s lymphoma (HL) disease, sino-nasal T-cell lymphomas, and others. Although lytic gene expression can contribute to the development of EBV-associated neoplasm, the exact role of EBV lytic cycle in the carcinogenic process is poorly understood at present. In contrast, it has been established that several viral latency proteins are unquestionably necessary for the oncogenic transformation. Interestingly, epigenetic modifications are revealed to play an important role in EBV-induced transformation. For example, the latent membrane protein 1 (LMP1)–induced hypermethylation repressed E-cadherin expression by inducing DNA methyltransferases DNMT1 3A and 3B, thereby positively affecting the tumor invasive capacity. Furthermore, LMP1 transcriptionally upregulates the histone demethylase KDM6B, which may contribute to the pathogenesis of HL. Epstein–Barr virus (EBV) nuclear protein 2 (EBNA2), a key determinant of primary B lymphocyte growth transformation, was shown to alter histone acetylation by interaction with p300/CBP complex to activate transcription. Therefore, understanding the interplay between EBV latent genes and epigenetic players could provide new insights about novel strategies to control viral infection. In fact, HDAC inhibitors such as sodium butyrate and TSA reproducibly activated EBV lytic cycle gene expression in the cellosaurus cell line HH514–6. Contrariwise, treatment with the same inhibitors did not induce the lytic cycle in marmoset B-cell line B95–8, which suggests the presence of a complementary activity besides histone deacytlation inhibition that is essential to disrupt EBV latency. Interestingly, treatment with DZNep, the inhibitor of H3K27me3 and H4K20me3, along with TSA, resulted in a significant induction of BZLF1 transcription required for the reactivation of the virus from latency. Furthermore, treatment with chaetocin, the specific H3K9 methyltransferase (Suv39 h1) inhibitor, transactivated BZLF1 gene in a dose–dependent manner in B95–8 cells but not in Akata or Raji cells. This suggests a cell type dependency in the mechanism of epigenetic silencing or reactivation succeeding histone modification of BZLF1 promoter. In this setting, it is of high importance to comprehend and decipher the mechanism by which the different epigenetic inhibitors, in particular HDAC inhibitors, can activate or repress the EBV lytic cycle. For example, valproic acid not only failed to induce the EBV lytic cycle in HH514–16 BL cells, but also blocked the induction of EBV early lytic proteins ZEBRA and EA-D in response to sodium butyrate and TSA treatment, illustrating thus a novel model of functional antagonism between HDAC inhibitors. A related point to consider is that the induction of EBV lytic-phase
gene expression by epigenetic manipulation along with antiviral drugs could exemplify a promising targeted therapeutic approach to manage EBV-associated lymphomas. Several HDAC inhibitors, including VPA, sodium butyrate, oxamflatin, and so on, effectively sensitized EBV+ lymphoma cells to ganciclovir, an approach known as “lytic induction therapy”. This sheds light on the potential use of those drugs as sensitizers to antivirals for the treatment of EBV-associated lymphomas and draws a new rational design of treatment regimens.

10.2.4 Kaposi's sarcoma-associated herpesvirus (KSHV)

Kaposi’s sarcoma-associated herpesvirus (KSHV) or human herpes virus 8 (HHV-8) infection is the causative agent of Kaposi’s sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman’s disease. Based on sequence homology, KSHV shares several properties with EBV. Thus the epigenetically repressed promoter of replication and transcription activator (RTA), indispensable for the lytic switch, could be reactivated through the use of HDAC inhibitors. This was evidenced by the productive viral reactivation and release of mature virions in vitro and in vivo (Fig. 10.1). In addition, PTC-209, a novel inhibitor of Bim1, a member of Polycomb repressive complex 1 that monoubiquitinates histone 2A on lysine residue 119 (H2AK119ub), also induced KSHV lytic gene expression in PEL cells (Fig. 10.2). It is noteworthy that since lytic proteins contribute to KSHV-mediated oncogenesis, the use of those drugs alone in the setting of KSHV-associated cancers could potentially lead to viral reactivation and spread to nearby cells. Thus adopting the concept of the previously mentioned “lytic induction therapy,” in which KSHV lytic cycle-inducer are combined with a second agent, could be beneficial. Indeed, using the proteasome/HDAC inhibitor combination therapy in PEL eradicated KSHV-infected PEL cells without increasing viremia in mice. This is reinforced by the fact that HDAC inhibitors demonstrated their ability to induce apoptotic cell death in the majority of cells latently infected with KSHV, which stresses on the fact that HDAC inhibitors may be an advantageous therapeutic option for patients with KSHV-mediated neoplasm.

10.2.5 Human papillomavirus (HPV)

Belonging to the Papillomaviridae family, human Papillomavirus (HPV) is a small double-stranded DNA virus that exhibits tropism for mucosal and cutaneous epithelia of the genital and upper respiratory tracts, as well as for the skin. With more than 100 HPV types identified, those strains are classified into nononcogenic low-risk (LR) or oncogenic high-risk (HR) HPV. While LR HPV is responsible of 90% of anogenital condyloma or genital warts, the persistent infection by HR HPV has the potential to advance into high-grade dysplasia and neoplastic transformation, including cervical, anogenital, and oropharyngeal cancers. In fact, the introduction of three FDA-approved HPV...
vaccines \cite{138} and the availability of various therapeutic options \cite{139} had drastically shifted the perception of HPV infection in terms of prevention, diagnosis, and treatment. Despite this, HPV-related diseases are still considered a major cause of morbidity and mortality \cite{140} as the pathogen remains a main causative player of infection-related cancer in both men and women. \cite{141} For instance, HPV-18 is considered a poor prognostic factor in stage I–IIA cervical cancer following primary surgical treatment, \cite{142} and persistent HPV-16 infection is correlated to the recurrence of high-grade cervical intraepithelial neoplasia. \cite{143} Knowing that advanced, recurrent, or metastatic cervical cancer share poor prognosis \cite{144} and that the available prophylactic vaccines do not impact preexisting infections, finding new therapeutic approaches to manage HPV infection is a vital need. In fact, abundant evidence substantiates the vital interplay between the HPV E6/E7 oncoproteins and histone-modifying enzymes to maintain persistent infection, induce cellular transformation, and/or promote invasiveness. \cite{145,146} By way of illustration, increased expression levels of EZH2 phosphorylated on serine 21 and KDM6A and reduced BMI1 protein in E6/E7-expressing human foreskin keratinocytes might be significant for cancer initiation and progression. \cite{147} E7 protein in HPV-31 binds to and inhibits HDACs, thus enhancing viral replication by activating E2F2 transcription. \cite{148} E6 oncoprotein inhibits p300-mediated acetylation on p53 and nucleosomal core histones, which mediates repression of p53 transactivation. \cite{149} Hence, targeting some members of the epigenetic machinery could play a role in controlling HPV infection and/or HPV-proneoplastic or neoplastic changes. The HDAC inhibitor vorinostat abrogated viral DNA amplification and host DNA replication. In addition, it significantly reduced the E7-induced DNA damage response as well as the E6- and E7-induced destabilization of the major tumor suppressor p53 and pRB proteins, respectively, which led to DNA damage and triggered apoptosis in HPV-18-infected primary human keratinocytes. Similar effect was also observed with belinostat and panobinostat, indicating that inhibition observed with vorinostat is not due to an off-target effect. \cite{32} Furthermore, sodium butyrate and TSA provoked intrinsic type II apoptosis by inducing the proapoptotic isoforms of p73 in HPV-16 E7-positive cervical carcinoma cells. \cite{26} Besides, growth inhibition of cervical carcinoma cells was shown with the use of the HDAC inhibitor phenylbutyrate (PB), independently of HPV type, copy number, or integration site. \cite{35} Sodium butyrate and TSA induced a block in G1 to S transition and subsequent apoptosis in HPV-18-positive cervical carcinoma cells despite ongoing E6/E7 gene expression (Fig. 10.1). \cite{27} Even though the use of valproate increased oncoprotein gene expression in vitro, E6 and E7 transcripts were mainly unchanged in primary tumors of patients with cervical cancer in addition to increased p53 transcription stabilization due to acetylation at lysines 273 and 282, which justify its potential use in HPV-related malignancies. \cite{150} It is worth mentioning that unlike other HDACs, HDAC 10 can suppress cervical cancer metastasis by suppressing matrix metalloproteinase (MMP) 2 expression as well as other genes recognized to be critical for cancer cell invasion and metastasis, which sheds light on the
significance of selecting/developing isoform-specific HDAC inhibitors in anticancer therapy. HDAC inhibitors have also been tested in combination with other agents. Combining TSA or vorinostat with the proteasome inhibitor bortezomib synergistically induced a caspase-mediated apoptosis in cervical cancer cells while sparing normal cells. This combination prolonged survival and slowed growth of a xenograft tumor in immunodeficient mice by an additive effect rather than synergy. Similarly, sodium butyrate, in combination with 7-hydroxy-stauroporine (UCN-01), a protein kinase C inhibitor with a potential antitumor spectrum, enhanced intrinsic apoptotic pathways in HPV-positive human cervical carcinoma cells through p53 and p73 signaling and inhibited tumor growth in xenografted nude mice. In line with this, phosphatidylinositol 3-kinase (PI3K) inhibitors wortmannin or LY294002 enhanced sodium butyrate-mediated apoptosis when used in combination through the activation of the caspase pathway in HPV-positive carcinoma cells. It may be noted that the EZH2 inhibitor DZNep was also tested in the context of HPV-positive oropharyngeal squamous cell carcinomas, where it displayed antiproliferative characteristics, highlighting its potential use to sensitize tumors to current chemotherapies or to limit cell differentiation. Taken together, manipulation of epigenetic players, with a special emphasis on HDAC inhibitors, appears to be an appealing target that could lead to enrichment of the therapeutic options array to control benign HPV infections and suppress progeny production and infectious transmission, as well as treat HPV-related dysplasia and carcinoma. This will be ensured by replicating in vitro results in predictive models and clinical trial studies with adapted experimental designs.

10.2.6 Polyomaviruses

The polyomavirus (PyV) family is composed of a number of related double-strand closed–circular DNA tumor viruses that include John Cunningham (JC), BK, and Merkel cell virus (MCV), in addition to other members. Existing as chromatin throughout its life cycle and in the nucleus of infected cells, viral genome is described to be a minichromosome subject to epigenetic regulation. For example, the acetyltransferases PCAF and GCN5 stimulate DNA replication by binding to and acetylating PyV large T antigen (PyLT), spotting their important role for replication in vivo. Moreover, another study showed that the expression of PyV small T antigen is sufficient to induce hyperacetylation at major sites of H3 and H4 associated with viral chromatin. Regulation by acetylation was also studied in the setting of JC virus, the etiological agent of a fatal demyelinating disease known as progressive multifocal leukoencephalopathy (PML). It has been demonstrated that the HDAC inhibitors TSA and butyrate can precipitate a 20– to 30-fold increase in JC virus early promoter activity in nonglial cells and 2-fold in glial cells in transiently and stably integrated viral promoter, which confirms the role of acetylation/deacetylation in the regulation of JC virus. Furthermore, the
same HDAC inhibitors stimulated early and late transcription of JC virus in human oligodendroglioma cells, and cotransfection with expression plasmid for the acetyltransferase p300 also stimulated the level of transcription (Fig. 10.1). Interestingly, JCV epigenetic regulation by acetylation appears to involve the NF-κB binding site in the JC virus non-coding control region (NCCR), as mutations in this region prevented NF-κB p65 binding and blocked the effect of TSA.28 As this is in line with the “shock and kill” strategy in HIV management, it could pave the way for the introduction of new therapeutic strategies to eliminate the pool of JC virus reservoirs. On the other hand, BK, a potential onco-genic virus to humans and the causative agent of polyomavirus-associated nephropathy (PVAN) and hemorrhagic cystitis (HC) in renal transplant recipients and bone marrow transplant patients, respectively,159 has also been shown to be subject to epigenetic modifications.160 BK virus minichromosome was identified to be hyperacetylated on histones 3, 2B, 2A, and 4, in addition to posttranslational modifications of various histones, for instance, methylation, phosphorylation, ubiquitination, and formylation.161 In line with this, the histone acetyltransferase GCN5 expression was demonstrated to be increased during BK virus infection, which promotes viral pathogenesis and replication in human proximal tubular epithelial cells. This effect was countered by the use of the histone acetyltransferase inhibitor CPTH2, which resulted in a significant decrease in the major capsid protein VP1 expression, a marker of BK virus infection. Interestingly, the use of DNA methyl transferase enzyme 1 inhibitor RG108 in the same experimental model significantly decreased BK virus DNA and disrupted epithelial to mesenchymal transition and fibrosis. This suggests that CPTH2 and RG108 could potentially serve as antiviral therapy in BK virus-associated nephropathy as they can block viral replication and reverse or prevent pathological disease progression.53 Alternatively, histone modification in the context of MCV, the causative agent for Merkel cell carcinoma (MCC), a rare, aggressive neuroendocrine malignancy,162 was also designated. It has been demonstrated that the viral small T antigen can bind to the histone acetyltransferase EP400, along with another cellular protein known as MYC homolog MYCL (L-MYC), where the ST-MYCL-EP400 complex activates gene promoter expression, and contributes thus to cellular transformation and generation of induced pluripotent stem (IPS) cells.163 Dysregulation in H3K27me3 mark was also noted in MCC, where a strong reduction of H3K27me3 correlates with large T antigen-positive Merkel cell carcinomas, which further attests to a link between epigenetic deregulation and pathogenesis of virus-positive Merkel cell carcinomas.164 As an interesting approach, combining SAHA with mithramycin A, a drug that has synergistic effects with HDAC inhibitors, reinduced the expression of MHC class I chain–related protein (MIC) in vitro and in vivo, rendering Merkel cell carcinoma (MCC) cells more sensitive to lysis by cytotoxic lymphocytes.42 This offers new potential therapeutic platforms where HDAC inhibitors could be combined with immune-modulating molecules to treat MCC. In addition, as several common characteristics are shared between human polyomaviruses, it will be of interest to investigate the
mechanisms responsible for epigenetic modifications and dissect the complex interplay between viral proteins and cellular contributors, as this may potentially lead to innovative treatments for therapeutic intervention.

10.2.7 Human T lymphotropic virus (HTLV)

The human T lymphotropic virus (HTLV) is the first human retrovirus discovered. With five to ten million HTLV-1-infected individuals, this pathogen is identified as the etiological agent behind adult T-cell leukemia/lymphoma (ATL) and tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM). Even though recent advances such as allogeneic hematopoietic stem cell transplantation and molecular targeted therapies have progressively improved the clinical outcomes in the context of ATL, the optimal treatment remains perplexing as no standard regimens are available. For instance, intensive chemotherapy has very limited benefit in aggressive ATL. In addition, treatment options and outcomes in the setting of relapsed or primary refractory ATL represent a specific challenge and are generally unsatisfactory. Thus a finer understanding of the mechanisms behind viral persistence, pathogenesis, and cellular transformation could identify novel targets, expand the repertoire of treatment options, and improve therapeutic outcomes. Thereafter, by being integrated into the cellular DNA and chromatinized, HTLV-1 provirus is subsequently subjected to genetic and epigenetic modulations such as selective DNA methylation and histone modifications, which rationalize the potential testing of some epigenetic modulators/inhibitors. Remarkably, the HDAC inhibitors SAHA, entinostat (MS-275), and panobinostat (LBH589) effectively inhibited the proliferation of both human HTLV-1-infected T cells and freshly isolated ATL cells harvested from patients. Moreover, induction of cell cycle arrest at the G2/M phase and apoptosis in infected cells was noted after treatment, mainly by inhibiting NF-B signaling. It is to be noted that panobinostat is currently under testing in a phase II trial for treating relapsed or refractory non-Hodgkin lymphoma, including recurrent ATL. In line with this, depsipeptide, another HDAC inhibitor, inhibited tumor growth and prolonged survival in a murine model of human ATL, with enhanced efficacy when combined with the monoclonal antibody daclizumab. The use of daclizumab was stopped in 2018 due to side effects such as encephalitis and meningencephalitis. On the other hand and in the management of TSP/HAM, the use of VPA was assessed (NCT00519181). This strategy aims to induce a transcriptional activation of the viral reservoir to expose the infected cells to the host immune response. Treatment with VPA transiently activated the latent viral reservoir causing its collapse in vitro, ex vivo, and in HAM/TSP patients at late clinical stages, providing a proof-of-concept for gene activation therapy (Fig. 10.1). In addition, VPA enhanced and prolonged Tax-mRNA expression, a viral protein responsible for viral transcription activation and considered a target for cytotoxic T lymphocytes (CTL) response. Also, VPA
increased the number of Tax-expressing provirus-positive cells, which might stimulate and expand Tax-specific CD8 T cells in asymptomatic HTLV-1 carriers-cultured lymphocytes and HAM/TSP patients. Nevertheless, even though treatment with HDAC inhibitors increased HTLV-1 gene expression, a decrease in CD8\(^+\) cell lytic efficiency was noted. This is possibly due to the fact that the broad-spectrum inhibition of HDAC might affect their regulatory role toward a wide variety of proteins, with a special emphasis on the role of HDAC6. Thus, undoubtedly, further studies are required to reveal the role of each player, keeping the antiviral clearance response in host-virus interactions as an endpoint.

### 10.3 Epidemic/emerging viral infections

During the past decades, emerging and pandemic viruses have gained much attention as they impose a major global public threat and continue to be a repetitive challenge. An enhanced understanding of the molecular and immunological aspect of such viral-host interplay is more than need as those pathogens are subject to rapid mutation and selection of new variants. In this special setting, epigenetics could offer new molecular insights, as well as novel therapeutic platforms.

#### 10.3.1 Influenza A virus (IAV)

Influenza A virus (IAV) is a very well-known human respiratory pathogen that should be given special attention for several reasons. First, and despite the fact that infection is primarily considered to be limited to the respiratory system where it can result in dramatic pulmonary complications and death, extrapulmonary complications such as myocarditis and encephalitis have been reported. Second, as this virus targets various hosts, including human, swine, and domestic poultry, the emergence of novel IAV strains is highly expected, which imposes a constant threat of the emergence of a new influenza pandemic like the 2009 global avian influenza outbreak. What adds a layer of complexity is the emergence of virus mutations that could precipitate resistance to the antiviral therapy, rendering it ineffective. In addition, current IAV vaccines induce only short-term seasonal immunity and no universal IAV vaccine is available. Therefore it is not surprising that each year 1 billion cases of flu, between 3 million and 5 million cases of severe illness, and 300,000 to 500,000 deaths are reported globally, based on the World Health Organization estimate. Without a doubt, this poses serious medical and economic losses: for example, the estimated annual economic burden of influenza in the United States was $11.2 billion in 2015. Hence, the development of novel antiinfluenza strategies with an alternative mechanism of action is the need of the hour, and again, epigenetic manipulations could constitute a part of this stratagem as various players are implicated in IAV infection. For instance, an increase in the methylation of lysine 79 of histone 3 was detected in influenza virus infected cells. The inhibition of Dot1L, the H3K79
methyltransferase with the inhibitor EPZ-5676, resulted in an increase in viral replication, which advocates a role of H3K79 methylation in controlling influenza virus infection (Fig. 10.2). Beside methylation, acetylation of the viral nucleoprotein (NP), whose function corresponds to that of eukaryotic histones by the two host acetyltransferases GCN5 and P300/CBP-associated factor (PCAF), regulated the polymerase activity in IAV. In addition, HDAC1 is demonstrated to inhibit IAV infection by being a vital part of host type I interferon (IFN)-mediated response against IAV. In contrast to this study, Chen et al. confirmed that HDAC1 could facilitate viral replication and that its depletion suppressed replication of IAV, pointing toward downregulation of HDAC1 levels as a potential strategy to control influenza virus. Apart from HDAC1, HDAC6 has been identified as a negative regulator of IAV infection through various mechanisms. By binding to and deacetylating the polymerase acidic protein (PA), an RNA polymerase subunit, HDAC6 inhibited the viral enzyme activity and subsequently suppressed virus RNA replication and transcription. Moreover, HDAC6 exhibited an anti-IAV activity by negatively regulating the trafficking of viral components to the site of virus assembly. In the light of what was mentioned, the potential development of HDAC6 modulators or stimulators to be used to amplify the anti-IAV potential of endogenous HDAC6 could constitute an alternative anti-IAV approach. However, it is indispensable to understand the interplay between IAV and the various HDACs at the molecular level to boost the development of such a strategy.

### 10.3.2 Coronaviruses (SARS-CoV, MERS-CoV, SARS-CoV-2)

Coronaviruses (CoVs) are a family of enveloped, nonsegmented positive-sense RNA viruses. Although described for the first time in 1949, CoVs gained much interest during the 2002–2003 severe acute respiratory syndrome (SARS)-CoV outbreak, the 2012 Middle East respiratory syndrome (MERS)-CoV outbreak and the 2019 SARS-CoV-2 epidemic, the later being identified as the etiological factor of the coronavirus disease 2019 (Covid-19). SARS-CoV, MERS-CoV, and SARS-CoV-2 are highly pathogenic agents that precipitate severe respiratory infection often associated with shock, acute kidney injury, coagulopathy, and ultimately death. To date, no antiviral drugs to target CoVs are available, which focuses the light on the necessity to develop new therapeutic agents to target and control those emerging pathogens as they hold a risk of reemergence due to their mutation and recombination ability, as well as their tropism to multiple cell type and species. Epigenetic modifications correlated with pathogenesis of CoVs are multiplex as SARS and MERS could induce distinct changes in the basal state of host chromatin during their pathologic process. By using a combination of virologic, transcriptomic, and proteomic data, it has been shown that CoVs can interfere with the interferon (IFN)-stimulated gene (ISG) response to ensure successful viral infection and replication: ISG expression was successively delayed by both SARS-CoV and MERS-CoV in infected human respiratory cell until peak viral titers had been reached, partly
due to the absence and delay of IFN induction. However, after this delay, a strong induction of ISG effectors due to H3K4me3 incorporation and H3K27me3 depletion was observed in the context of SARS-CoV, while MERS-CoV significantly inhibited the expression of specific ISG subsets through H3K27me3 enrichment and H3K4me3 depletion (Fig. 10.2). Interestingly, this viral antagonistic approach in the setting of MERS-CoV is shared with the influenza A virus, strain Vietnam/1203/2004 also referred to as H5N1-VN1203, which could point toward conserved mechanisms employed by unrelated respiratory viral pathogens to manipulate and control the global ISG responses. In line with this, both MERS-CoV and H5N1-VN1203 downregulated IFNγ-associated antigen-presentation gene expression through epigenetic modulation, namely, DNA methylation, rather than histone modification for MERS-CoV. Although limited, this suggests that multiple epigenetic modifications are involved in viral-induced modulation of host immunity and spots common molecular approaches utilized by two diverse viral families. Additional studies are needed to reveal supplementary aspects of epigenetic modification and link them with additional definite aspects of immunity, comprising inflammatory responses and apoptosis, and translate those datasets to the level of vaccines and therapeutic treatment development.

### 10.3.3 Arboviruses

Arboviruses or arthropod-borne viruses constitute an important section of the emerging infectious pathogens. Those include Zika virus (ZIKV), dengue virus (DENV), West Nile virus (WNV), yellow fever virus (YFV), and chikungunya virus (CHIKV). Emergence and reemergence of such vectors is considered to be a major health concern due to the subsequent global outbreak. This is aggravated by their rapid and geographically extensive expansion and dispersal worldwide. What adds a layer of complexity is lack of effective definitive treatment, although multiple vaccine candidates have shown promise for DENV. This stresses the need to introduce innovative drugs to control future outbreaks of emerging arboviruses. Unlike other viruses, epigenetic data regarding histone modification is limited, although other epigenetic modifications associated with arbovirus infections, for instance, microRNAs and DNA methylation, are much more abundant. However, it has been shown that the methyltransferase inhibitor GSK126 suppresses the infection of ZIKV, which may deliver a primary therapeutic option for new or emerging pathogens (Fig. 10.2). In addition, and in the context of impaired neuronal homeostasis precipitated during ZIKV infection, it has been shown that growth inhibition of human neural stem cells (hNSCs) can be induced by increasing serine 139 phosphorylation of histone H2AX (γH2AX) upon infection with the strain MR766, or, alternatively, by upregulating serine 15 phosphorylation of p53, p21, and PUMA with the strain PRVABC59, while inducing immature neuroprogenitor cell death during early differentiation. As yet unrevealed potential epigenetic-related ZIKV-induced damage mechanisms may ease the identification of future therapeutic
targets. On the other hand, the HDAC inhibitor valproic acid significantly reduced the secretion of inflammatory cytokines, namely, IL-8, IL-1b, IL-6, and TNF-alpha, and also of the TH2 cytokine IL-10 in human monocyte-derived macrophages (MDMs) infected with DENV-2 serotype. In this context, it is important to take into account the association of histone function with DENV infection, where it has been shown that DENV-capsid protein (C) can bind to the nuclear histone proteins H2A, H2B, H3, and H4 and act as a histone mimic, which could disrupt nucleosome formation and normal host cell homeostasis in favor of viral replication. This has also been shown in the context of yellow fever virus, where the core viral protein displays an impressive homology to the histone H4 as well as other histone proteins, in addition to its ability to undergo acetylation and bind to nuclear proteins, which could point to shared properties between arboviruses. Alternatively, VPA induced a complete inhibition in the virus yield in the setting of WNV infection with an important blockage of WNV RNA replication and translation. Combining SAHA, another HDAC inhibitor, with NITD008, an adenosine analogue inhibitor, decreased the mRNA levels of inflammatory cytokines and improved disease outcome by reducing neuronal death during WNV-established CNS infection in C57BL/6 mice (Fig. 10.1). Thus given that data regarding epigenetic regulation of arboviruses is scarce, further studies covering a wider range of arboviruses are definitively desired to address the host–viral interplay and uncover subsequent therapeutic platforms that might generate potential antiviral candidates alone or as adjuvant in combined therapies.

### 10.3.4 Ebola virus

Ebola virus (EBOV), the etiological agent of Ebola hemorrhagic fever, is considered one of the most virulent pathogens responsible for more than 20 outbreaks in Africa, with the most important epidemic reported in 2014. The unprecedented spread and size of this outbreak has warranted an urgent need to understand the viral evasion mechanisms and pathogenesis to develop and evolve new strategies with an endpoint of preventing or minimizing the burden of such emerging infectious disease. Belonging to the Filoviridae family, EBOV is a single-stranded negative-sense RNA virus that encodes at least eight distinct proteins. Data about epigenetic histone regulation of the latter is scarce. However, it is known that EBOV nucleoprotein (NP) and the viral glycoprotein protein VP40, involved in transcription and replication of the viral genome and nucleocapsid formation, respectively, are acetylated in their functional domains by eukaryotic HATs, including P300/CREB-binding protein (P300/CBP) and P300/CBP-associated factor (PCAF), in vitro. Interestingly, SMYD3, a histone-lysine N-methyltransferase that plays a vital role in transcriptional activation by being a member of the RNA polymerase complex, was recognized to interact with Ebolavirus NP, suggesting its potential role in modulation of the transcriptional activity of vRNA and mRNA. It should
be noted that an interplay exists between EBOV proteins and various posttranslational modifications: VP30 phosphorylation modulates both viral transcription and replication, VP35 blocks IFN production in innate immune cells by exploiting the host SUMO modification machinery, and predication of the potential viral miRNA target genes points toward their role in silencing and downregulating central genes related to host cell defense mechanism and antiviral response systems. However, those modifications will not be discussed here since this is beyond the scope of this chapter. In its entirety, preliminary insights in relation with posttranslational modifications are still modest, limiting our perception of the epigenetic molecular mechanisms regulating EBOV infection. Fortunately, novel interactions between EBOV and the host are to be revealed through continuous research, elucidating a more detailed molecular dissection of this fatal infection and thus effective EBOV disease treatment.

10.3.5 Bornavirus

Being a negative single-stranded RNA pathogen, Borna disease virus (BDV) is the etiological agent behind Borna disease, a central nervous system (CNS) disease characterized by encephalitis and significant behavioral abnormalities, although its ability to infect humans is still a matter of controversy. In fact, BDV replicates and persists in the cellular compartment of the nervous system, comprising neurons, astrocytes, and oligodendrocytes, in addition to nonneural cells, namely, peripheral blood mononuclear and bone marrow cells. Since BDV closely associates with chromatin and persists in the cell nucleus, this pathogen had developed various mechanisms to manipulate cellular chromatin, with the end goal of ensuring survival and propagation. At the epigenetic level, histone lysine acetylation is impacted in BDV-infected oligodendroglial (OL) cells. For instance, two HATs (GCN5 and PCAF) were downregulated, and four HDACs (SIRT1, SIRT2, HDAC4, and HDAC7) were found to be upregulated, possibly impacting the host proteome profile and lowering host gene expression (Fig. 10.1). In line with this, BDV infection affects the acetylation of several lysine acetyltransferases (KAT) in a nonimmortalized rat oligodendrocyte precursor line, as well as the acetylation of proteins involved in butanoate, fatty acid, and amino acid metabolism in addition to membrane-associated proteins and transmembrane transporter activity. This facilitates energy-demanding processes such as shuttling of viral proteins to and from nuclear replication sites, which could contribute to BDV persistence. It has been speculated that BDV phosphoprotein (P) is the key determinant of such changes where a decrease of H2B and H4 acetylation on nominated lysine residues was detected after BDV infection in primary cultures of cortical neurons. Furthermore, a decreased level of H3K9 histone acetylation was also demonstrated in BDV-1-infected primary cultures of hippocampal neurons and rat models, with a precipitated spatial memory impairment
and cognitive deficits. Intriguingly, the use of SAHA can counteract the damaging effects of BDV-1 on synaptic plasticity in terms of impairments in spatial memory and hippocampal functions.\textsuperscript{34} Taken together, BDV–induced cognitive impairment could establish an interesting model to study and evaluate the interplay between viral infection and its subsequent impact on epigenetic signaling in neurons, and most importantly the role that epigenetics modulators/inhibitors could play to reverse/control those effects.

### 10.4 Conclusion and future perspectives

By undergoing diverse posttranslational modifications, histone proteins could influence various cellular functions and set up an important trait of epigenetics. In fact, the development of novel techniques, such as high-throughput sequencing and chromatin immunoprecipitation, not only added to our understanding about the host–virus interplay, but also opened the door toward newer therapeutic modalities. As histone modifications play critical roles in regulating the life cycle of viruses, those complexes have become appealing targets to project new innovative broad-spectrum antivirals. In fact, this new therapeutic modality offers the advantage of targeting the very early stage of viral infection, in contrast to the currently present antivirals that target DNA polymerase during the initiation of the infection or reactivation, which could prevent the immunopathological effect of some expressed IE genes, like in HCMV infection.\textsuperscript{220} Moreover, as those “epidrugs” target the host rather than viral components, the emergence of strains that can develop drug resistance or hijack and manipulate the host machinery to escape immune surveillance is minimized. Besides, as those agents are disclosing new horizons in various viral infection, their use in coinfection scenario (e.g. HCMV-HSV, HIV-HCV) could be addressed, alone or in combination with the preexisting antivirals. Despite this wide array of encouraging substantiation, unintended systemic off-target effects and restriction in tissue-specific drug delivery are considered major limitations for epigenetic therapy applicability. Another aspect is the off-target reactivation of dormant viruses, such as the use of HDAC inhibitor–induced coxsackievirus B3 replication and precipitated apoptosis, aggravating viral myocarditis.\textsuperscript{221} These barriers could be circumvented by dissecting the complex epigenetic machinery that introduces and modulates those modification to characterize the cellular contributors as well as the viral proteins in question and complementing this in-depth analysis by in vitro and in vivo exploration. Moreover, the contribution of the less considered posttranslational modifications such as phosphorylation or sumoylation should be portrayed. On the whole, improving our understanding of the pathogenesis of viral infection and the virus–host interplay from the standpoint of epigenetic regulation will enhance this novel modality as an innovative therapeutic tool, as well as potential method of prevention.
References

1. Balakrishnan L, Milavetz B. Epigenetic regulation of viral biological processes. *Viruses*. 2017;9:346. https://doi.org/10.3390/v9110346.

2. Li S, Kong L, Yu X, Zheng Y. Host-virus interactions: from the perspectives of epigenetics. *Rev Med Virol*. 2014;24:223–241. https://doi.org/10.1002/rmv.1783.

3. Lieberman PM. Chromatin organization and virus gene expression. *J Cell Physiol*. 2008;216:381–395. https://doi.org/10.1002/jcp.21421.

4. Paschos K, Allday MJ. Epigenetic reprogramming of host genes in viral and microbial pathogenesis. *Trends Microbiol*. 2010;18:439–447. https://doi.org/10.1016/j.tim.2010.07.003.

5. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. *Cell Res*. 2011;21:381–395. https://doi.org/10.1038/cr.2011.22.

6. Milavetz BI, Balakrishnan L. Viral epigenetics. *Methods Mol Biol*. 2015;1238:569–596. https://doi.org/10.1007/978-1-4939-1804-1_30.

7. Le Douce V, Herbein G, Rohr O, Schwartz C. Molecular mechanisms of HIV-1 persistence in the monocyte–macrophage lineage. *Retrovirology*. 2010;7:32. https://doi.org/10.1186/1742-4690-7-32.

8. Nehme Z, Pasquereau S, Herbein G. Control of viral infections by epigenetic–targeted therapy. *Clin Epigenetics*. 2019;11:55. https://doi.org/10.1186/s13148-019-0654-9.

9. Churchill MJ, Deeks SG, Margolis DM, Siliciano RF, Swanstrom R. HIV reservoirs: what, where and how to target them. *Nat Rev Microbiol*. 2016;14:55–60. https://doi.org/10.1038/nrmicro.2015.5.

10. Van Lint C, Bouchat S, Marcello A. HIV-1 transcription and latency: an update. *Retrovirology*. 2013;10:67. https://doi.org/10.1186/1742-4690-10-67.

11. Kumar A, Darcis G, Van Lint C, Herbein G. Epigenetic control of HIV-1 post integration latency: implications for therapy. *Clin Epigenetics*. 2015;7:103. https://doi.org/10.1186/s13148-015-0137-6.

12. Darcis G, Van Driessche B, Van Lint C. HIV latency: should we shock or lock? *Trends Immunol*. 2017;38:217–228. https://doi.org/10.1016/j.it.2016.12.003.

13. Deeks SG. HIV: shock and kill. *Nature*. 2012;487:439–440. https://doi.org/10.1038/487439a.

14. Bose P, Dai Y, Grant S. Histone deacetylase inhibitor (HDACI) mechanisms of action: emerging insights. *Pharmacol Ther*. 2014;143:323–336. https://doi.org/10.1016/j.pharmthera.2014.04.004.

15. Michaelis M, Suhan T, Reinisch A, et al. Increased replication of human cytomegalovirus in retinal pigment epithelial cells by valproic acid depends on histone deacetylase inhibition. *Invest Ophthalmol Vis Sci*. 2005;46:3451–3457. https://doi.org/10.1177/105119410527947.

16. Pollicino T, Belloni L, Raffa G, et al. Hepatitis B virus replication is regulated by the acetylation status of hepatitis B virus cccDNA-bound H3 and H4 histones. *Gastroenterology*. 2006;130:823–837. https://doi.org/10.1053/j.gastro.2006.01.001.

17. Lezin A, Gillet N, Olindo S, et al. Histone deacetylase mediated transcriptional activation reduces proviral loads in HTLV-1 associated myelopathy/tropical spastic paraparesis patients. *Blood*. 2007;110:3722–3728. https://doi.org/10.1182/blood-2007-04-085076.

18. Azran I, Schavinsky-Khrapunsky Y, Aboud M. Role of tax protein in human T-cell leukemia virus type-I leukemogenicity. *Retrovirology*. 2004;1:20. https://doi.org/10.1186/1742-4690-1-20.

19. Belrose G, Gross A, Olindo S, et al. Effects of valproate on tax and HBZ expression in HTLV-1 and HAM/TSP T lymphocytes. *Blood*. 2011;118:2483–2491. https://doi.org/10.1182/blood-2010-11-321364.

20. Delgado FG, Cárdenas P, Castellanos JE. Valproic acid downregulates cytokine expression in human macrophages infected with dengue virus. *Diseases*. 2018;6:59. https://doi.org/10.3390/diseases6030059.

21. Vázquez-Calvo Á, Saiz J-C, Sobrino F, Martín-Acebes MA. Inhibition of enveloped virus infection of cultured cells by Valproic acid. *J Virol*. 2011;85:1267–1274. https://doi.org/10.1128/JVI.01717-10.

22. Huang Y, Tang Q, Nguyen M, Dulal K, Wang W, Zhu H. Histone deacetylase 3, not histone deacetylase 2, interacts with the major immediate early locus of human cytomegalovirus. *Virol J*. 2011;8:151. https://doi.org/10.1186/1743-422X-8-151.

23. Meier JL. Reactivation of the human cytomegalovirus major immediate-early regulatory region and viral replication in embryonal NTera2 cells: role of trichostatin a, retinoic acid, and deletion of the 21-base-pair repeats and modulator. *J Virol*. 2001;75:1581–1593. https://doi.org/10.1128/JVI.75.4.1581-1593.2001.
24. Feng Q, Su Z, Song S, et al. Histone deacetylase inhibitors suppress RSV infection and alleviate virus-induced airway inflammation. *Int J Mol Med*. 2016;38:812–822. https://doi.org/10.3892/ijmm.2016.2691.

25. Miller G, El-Guindy A, Countryman J, Ye J, Gradoville L. Lytic cycle switches of oncogenic human gammaherpesviruses. *Adv Cancer Res*. 2007;97:81–109. https://doi.org/10.1016/S0065-230X(06)97004-3.

26. Finzer P, Krueger A, Stöhr M, et al. HDAC inhibitors trigger apoptosis in HPV-positive cells by inducing the E2F-p73 pathway. *Oncogene*. 2004;23:4807–4817. https://doi.org/10.1038/sj.onc.1207620.

27. Finzer P, Kunzten C, Soto U, zur Hausen H, Rössl F. Inhibitors of histone deacetylase arrest cell cycle and induce apoptosis in cervical carcinoma cells circumventing human papillomavirus oncogene expression. *Oncogene*. 2001;20:4768–4776. https://doi.org/10.1038/sj.onc.1204652.

28. Wollebo HS, Woldemichele B, Khalili K, Safak M, White MK. Epigenetic regulation of polyomavirus JC. *Virol J*. 2013;10:264. https://doi.org/10.1186/1743-422X-10-264.

29. Wang Y-C, Yang X, Xing L-H, Kong W-Z. Effects of SAHA on proliferation and apoptosis of hepatocellular carcinoma cells and hepatitis B virus replication. *World J Gastroenterol*. 2013;19:5159–5164. https://doi.org/10.3748/wjg.v19.i31.5159.

30. Sato A, Saito Y, Sugiyama K, et al. Suppressive effect of the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) on hepatitis C virus replication. *J Cell Biochem*. 2013;114:1987–1996. https://doi.org/10.1002/jcb.24541.

31. Zhou Y, Wang Q, Yang Q, et al. Histone deacetylase 3 inhibitor suppresses hepatitis C virus replication by regulating Apo-A1 and LEAP-1 expression. *Virol Sin*. 2018;33:418–428. https://doi.org/10.1007/s12250-018-0057-7.

32. Banerjee NS, Moore DW, Broker TR, Chow LT. Vorinostat, a pan-HDAC inhibitor, abrogates productive HPV-18 DNA amplification. *Proc Natl Acad Sci USA*. 2018;115:E11138–E11147. https://doi.org/10.1073/pnas.1801156115.

33. Nishioka C, Ikezoe T, Yang J, et al. Histone deacetylase inhibitors induce growth arrest and apoptosis of HTLV-1-infected T-cells via blockade of signaling by nuclear factor kappaB. *Leuk Res*. 2008;32:287–296. https://doi.org/10.1016/j.leukres.2007.05.026.

34. Jie J, Xu X, Xia J, et al. Memory impairment induced by Borna disease virus 1 infection is associated with reduced H3K9 acetylation. *Cell Physiol Biochem*. 2018;49:381–394. https://doi.org/10.1159/000492890.

35. Finzer P, Stöhr N, Seibert N, Rössl F. Phenylbutyrate inhibits growth of cervical carcinoma cells independent of HPV type and copy number. *J Cancer Res Clin Oncol*. 2003;129:107–113. https://doi.org/10.1007/s00432-003-0416-z.

36. Kozlov MV, Kleymenova AA, Konduktorov KA, Malikova AZ, Kochetkov SN. Selective inhibitor of histone deacetylase 6 (tubastatin a) suppresses proliferation of hepatitis C virus replicon in culture of human hepatocytes. *Biochemistry (Mosq)*. 2014;79:637–642. https://doi.org/10.1134/S0006297914070050.

37. Chen J, Zhang M, Ju W, Waldmann TA. Effective treatment of a murine model of adult T-cell leukemia using depsipeptide and its combination with unmodified daclizumab directed toward CD25. *Blood*. 2009;113:1287–1293. https://doi.org/10.1182/blood-2008-04-149658.

38. Murata T, Kondo Y, Sugimoto A, et al. Epigenetic histone modification of Epstein-Barr virus BZLF1 promoter during latency and reactivation in Raji cells. *J Virol*. 2012;86:4752–4761. https://doi.org/10.1128/JVI.02911-11.

39. Bhatt S, Ashlock BM, Toomney NL, et al. Efficacious proteasome/HDAC inhibitor combination therapy for primary effusion lymphoma. *J Clin Invest*. 2013;123:2616–2628. https://doi.org/10.1172/JCI64503.

40. Lin Z, Bazzaro M, Wang M-C, Chan KC, Peng S, Roden RBS. Combination of proteasome and HDAC inhibitors for uterine cervical cancer treatment. *Clin Cancer Res*. 2009;15:570–577. https://doi.org/10.1158/1078-0432.CCR-08-1813.

41. Decrion-Barthod A-Z, Bosset M, Plissonnier M-L, et al. Sodium butyrate with UCN-01 has marked antitumour activity against cervical cancer cells. *Anticancer Res*. 2010;30:4049–4061.

42. Ritter C, Fan K, Paulson KG, Nghiem P, Schrama D, Becker JC. Reversal of epigenetic silencing of MHC class I chain-related protein A and B improves immune recognition of Merkel cell carcinoma. *Sci Rep*. 2016;6:21678. https://doi.org/10.1038/srep21678.
43. Nelson J, Roe K, Orillo B, Shi P-Y, Verma S. Combined treatment of adenosine nucleoside inhibitor NITD008 and histone deacetylase inhibitor vorinostat represents an immunotherapy strategy to ameliorate West Nile virus infection. *Antiviral Res.* 2015;122:39–45. https://doi.org/10.1016/j.antiviral.2015.07.008.

44. Bullen CK, Laird GM, Durand CM, Siliciano JD, Siliciano RF. Novel ex vivo approaches distinguish effective and ineffective single agents for reversing HIV-1 latency in vivo. *Nat Med.* 2014;20:425–429. https://doi.org/10.1038/nm.3489.

45. Søgaard OS, Graversen ME, Leth S, et al. The depsipeptide romidepsin reverses HIV-1 latency in vivo. *PLoS Pathog.* 2015;11. https://doi.org/10.1016/j.antiviral.2015.07.008.

46. Jønsson KL, Tolstrup M, Vad-Nielsen J, et al. Histone deacetylase inhibitor romidepsin inhibits de novo HIV-1 infections. *Antimicrob Agents Chemother.* 2015;59:3984–3994. https://doi.org/10.1128/ AAC.00574-15.

47. Archin NM, Liberty AL, Kashuba AD, et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. *Nature.* 2012;487:482–485. https://doi.org/10.1038/nature11286.

48. Tripathy MK, McManamy MEM, Burch BD, Archin NM, Margolis DM. H3K27 demethylation at the proviral promoter sensitizes latent HIV to the effects of vorinostat in ex vivo cultures of resting CD4+ T cells. *J Virol.* 2015;89:8392–8405. https://doi.org/10.1128/JVI.00572-15.

49. Bouchat S, Gatot J-S, Kabeya K, et al. Histone methyltransferase inhibitors induce HIV-1 recovery in resting CD4+ T cells from HIV-1-infected HAART-treated patients. *AIDS.* 2012;26:1473–1482. https://doi.org/10.1097/QAD.0b013e32835535f5.

50. Imai K, Togami H, Okamoto T. Involvement of histone H3 lysine 9 (H3K9) methyltransferase G9a in the maintenance of HIV-1 latency and its reactivation by BIX01294. *J Biol Chem.* 2010;285:16538–16545. https://doi.org/10.1074/jbc.M110.103531.

51. Friedman J, Cho W-K, Chu CK, et al. Epigenetic silencing of HIV-1 by the histone H3 lysine 27 methyltransferase enhancer of Zeste 2. *J Virol.* 2011;85:9078–9089. https://doi.org/10.1128/JVI.00836-11.

52. Imai K, Kamio N, Cueno ME, et al. Role of the histone H3 lysine 9 methyltransferase Suv39 h1 in maintaining Epstein-Barr virus latency in B95-8 cells. *FEBS J.* 2014;281:2148–2158. https://doi.org/10.1111/febs.12768.

53. Arbuckle JH, Gardina PJ, Gordon DN, et al. Inhibitors of the histone methyltransferases EZH2/1 induce a potent antiviral state and suppress infection by diverse viral pathogens. *MBio.* 2017;8. https://doi.org/10.1128/mBio.01141-17.

54. Abraham CG, Kulesza CA. Polycomb repressive complex 2 silences human cytomegalovirus transcription in quiescent infection models. *J Virol.* 2013;87:13193–13205. https://doi.org/10.1128/JVI.02420-13.

55. Lindsay CD, Kostiuk MA, Harris J, O’Connell DA, Seikaly H, Biron VL. Efficacy of EZH2 inhibitory drugs in human papillomavirus-positive and human papillomavirus-negative oropharyngeal squamous cell carcinomas. *Clin Epigenetics.* 2017;9:95. https://doi.org/10.1186/s13148-017-0390-y.

56. Marcos-Villar L, Dı´az-Colunga J, Sandoval J, et al. Epigenetic control of influenza virus: role of H3K79 methylation in interferon-induced antiviral response. *Sci Rep.* 2018;8:1230. https://doi.org/10.1038/s41598-018-19370-6.

57. Liang Y, Quenelle D, Vogel JL, Mascaro C, Ortega A, Kristie TM. A novel selective LSD1/KDM1A inhibitor epigenetically blocks herpes simplex virus lytic replication and reactivation from latency. *MBio.* 2013;4. https://doi.org/10.1128/mBio.00558-12.

58. Hill JM, Quenelle DC, Cardin RD, et al. Inhibition of LSD1 reduces herpesvirus infection, shedding, and recurrence by promoting epigenetic suppression of viral genomes. *Sci Transl Med.* 2014;6. https://doi.org/10.1126/scitranslmed.3010643.
61. Liang Y, Vogel JL, Arbuckle J, et al. Targeting the JMJD2 histone demethylases to epigenetically control herpesvirus infection and reactivation from latency. *Sci Transl Med*. 2013;5. https://doi.org/10.1126/scitranslmed.3005145.

62. Ptaschinski C, Mukherjee S, Moore ML, et al. RSV-induced H3K4 demethylase KDM5B leads to regulation of dendritic cell-derived innate cytokines and exacerbates pathogenesis in vivo. *PLoS Pathog*. 2015;11. https://doi.org/10.1371/journal.ppat.1004978.

63. Hopcraft SE, Pattenden SG, James LI, Frye S, Dittmer DP, Damania B. Chromatin remodeling controls Kaposi’s sarcoma-associated herpesvirus reactivation from latency. *PLoS Pathog*. 2018;14. https://doi.org/10.1371/journal.ppat.1007267.

64. Weller SK, Coen DM. Herpes simplex viruses: mechanisms of DNA replication. *Cold Spring Harb Perspect Biol*. 2012;4. https://doi.org/10.1101/cshperspect.a013011.

65. Looker KJ, Magaret AS, May MT, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012. *PLoS One*. 2015;10. https://doi.org/10.1371/journal.pone.0140765.

66. Wald A, Corey L. Persistence in the population: epidemiology, transmission. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, et al., eds. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press; 2007, Chapter 36.

67. Nicoll MP, Proença JT, Efstatiou S. The molecular basis of herpes simplex virus latency. *FEMS Microbiol Rev*. 2012;36:684–705. https://doi.org/10.1111/j.1574-6976.2011.00320.x.

68. Thellman NM, Triezenberg SJ. Herpes simplex virus establishment, maintenance, and reactivation: in vitro modeling of latency. *Pathogens*. 2017;6:28. https://doi.org/10.3390/pathogens6030028.

69. Knipe DM, Cliffe A. Chromatin control of herpes simplex virus lytic and latent infection. *Nat Rev Microbiol*. 2008;6:211–221. https://doi.org/10.1038/nrmicro1794.

70. Narayanan A, Ruyechan WT, Kristie TM. The coactivator host cell factor-1 mediates Set1 and MLL1 H3K4 trimethylation at herpesvirus immediate early promoters for initiation of infection. *Proc Natl Acad Sci USA*. 2007;104:10835–10840. https://doi.org/10.1073/pnas.0704351104.

71. Shi Y, Lan F, Matson C, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell*. 2004;119:941–953. https://doi.org/10.1016/j.cell.2004.12.012.

72. Klose RJ, Yamane K, Bae Y, et al. The transcriptional repressor JHDM3A demethylates trimethyl histone H3 lysine 9 and lysine 36. *Nature*. 2006;442:312–316. https://doi.org/10.1038/nature04853.

73. Cliffe AR, Arbuckle JH, Vogel JL, et al. Neuronal stress pathway mediating a histone methyl/phospho switch is required for herpes simplex virus reactivation. *Cell Host Microbe*. 2015;18:649–658. https://doi.org/10.1016/j.chom.2015.11.007.

74. Schottstedt V, Blümel J, Burger R, et al. Human cytomegalovirus (HCMV)—revisted*. *Transfus Med Hemonther*. 2010;37:365–375. https://doi.org/10.1159/000322141.

75. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol*. 2010;20:202–213. https://doi.org/10.1002/rmv.655.

76. Boeckh M, Geballe AP. Cytomegalovirus: pathogen, paradigm, and puzzle. *J Clin Invest*. 2011;121:1673–1680. https://doi.org/10.1172/JCI145449.

77. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. 2007;17:355–363. https://doi.org/10.1002/rmv.544.

78. Prichard MN, Kern ER. The search for new therapies for human cytomegalovirus infections. *Virus Res*. 2011;157:212–221. https://doi.org/10.1016/j.virusres.2010.11.004.

79. Clement M, Humphreys IR. Cytokine-mediated induction and regulation of tissue damage during cytomegalovirus infection. *Front Immunol*. 2019;10:78. https://doi.org/10.3389/fimmu.2019.00078.

80. Leng SX, Kamil J, Purdy JG, Lemmermann NA, Reddehase MJ, Goodrum FD. Recent advances in CMV tropism, latency, and diagnosis during aging. *GeroScience*. 2017;39:251–259. https://doi.org/10.1007/s11357-017-9985-7.

81. Dupont L, Reeves MB. Cytomegalovirus latency and reactivation: recent insights into an age old problem. *Rev Med Virol*. 2016;26:75–89. https://doi.org/10.1002/rmv.1862.
82. O’Connor CM, DiMaggio PA, Shenk T, Garcia BA. Quantitative proteomic discovery of dynamic epigenome changes that control human cytomegalovirus (HCMV) infection. *Mol Cell Proteomics*. 2014;13:2399–2410. https://doi.org/10.1074/mcp.M114.039792.

83. Rossetto CC, Tarrant-Elorza M, Pari GS. Cis and trans acting factors involved in human cytomegalovirus experimental and natural latent infection of CD14 (+) monocytes and CD34 (+) cells. *PLoS Pathog*. 2013;9. https://doi.org/10.1371/journal.ppat.1003366.

84. Abraham CG, Kulesza CA. Polycomb repressive complex 2 targets murine cytomegalovirus chromatin for modification and associates with viral replication centers. *PLoS One*. 2012;7. https://doi.org/10.1371/journal.pone.0029410.

85. Tan J, Yan Y, Wang X, Jiang Y, Xu HE. EZH2: biology, disease, and structure-based drug discovery. *Acta Pharmacol Sin*. 2014;35:161–174. https://doi.org/10.1038/aps.2013.161.

86. Svrlanska A, Reichel A, Schilling E-M, Scherer M, Stamminger T, Reuter N. A noncanonical function of polycomb repressive complexes promotes human cytomegalovirus lytic DNA replication and serves as a novel cellular target for antiviral intervention. *JV i r o l*. 2019;93. https://doi.org/10.1128/JVI.02143-18.

87. Cuevas-Bennett C, Shenk T. Dynamic histone H3 acetylation and methylation at human cytomegalovirus promoters during replication in fibroblasts. *J Virol*. 2008;82:9525–9536. https://doi.org/10.1128/JVI.00946-08.

88. Herbein G, Wendling D. Histone deacetylases in viral infections. *Clin Epigenetics*. 2010;1:13–24. https://doi.org/10.1007/s13148-010-0003-5.

89. Meng J, Stobart CC, Hotard AL, Moore ML. An overview of respiratory syncytial virus. *PLoS Pathog*. 2014;10. https://doi.org/10.1371/journal.ppat.1004016.

90. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*. 2010;375:1545–1555. https://doi.org/10.1016/S0140-6736(10)60206-1.

91. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005;352:1749–1759. https://doi.org/10.1056/NEJMoa043951.

92. Morales-Sánchez A, Fuentes-Panana EM. Human viruses and cancer. *Viruses*. 2014;6:4047–4079. https://doi.org/10.3390/v6104047.

93. Luo GG, Ou JJ. Oncogenic viruses and cancer. *Virol Sin*. 2015;30:83–84. https://doi.org/10.1007/s12250-015-3599-y.

94. Pan CQ, Zhang JX. Natural history and clinical consequences of hepatitis B virus infection. *Int J Med Sci*. 2005;2:36–40.

95. Peters MG, Hepatitis B. Virus infection: what is current and new. *Top Antivir Med*. 2019;26:112–116.

96. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012;30:2212–2219. https://doi.org/10.1016/j.vaccine.2011.12.116.

97. Inoue J, Ueno Y, Shimosegawa T. Management of chronic hepatitis B patients: efficacy & limitation of nucleos(t)ide analogues. *Indian J Med Res*. 2011;133:11–13.

98. Hensel KO, Rendon JC, Navas M-C, Rots MG, Postberg J. Virus-host interplay in hepatitis B virus infection and epigenetic treatment strategies. *FEBS J*. 2017;284:3550–3572. https://doi.org/10.1111/febs.14094.

99. Ren J-H, Hu J-L, Cheng S-T, et al. SIRT3 restricts hepatitis B virus transcription and replication through epigenetic regulation of covalently closed circular DNA involving suppressor of variegation 3-9 homolog 1 and SET domain containing 1A histone methyltransferases. *Hepatology*. 2018;68:1260–1276. https://doi.org/10.1002/hep.29912.

100. Rivière L, Gerossier L, Ducroux A, et al. HBx relieves chromatin-mediated transcriptional repression of hepatitis B viral cccDNA involving SETDB1 histone methyltransferase. *J Hepatol*. 2015;63:1093–1102. https://doi.org/10.1016/j.jhep.2015.06.023.

101. Belloni L, Pollicino T, De Nicola F, et al. Nuclear HBx binds the HBV minichromosome and modifies the epigenetic regulation of cccDNA function. *Proc Natl Acad Sci USA*. 2009;106:19975–19979. https://doi.org/10.1073/pnas.0908365106.
102. Ritchie D, Piekarz RL, Blombery P, et al. Reactivation of DNA viruses in association with histone deacetylase inhibitor therapy: a case series report. *Haematologica*. 2009;94:1618–1622. https://doi.org/10.3324/haematol.2009.008607.

103. Barbarotta L, Hurley K. Romidepsin for the treatment of peripheral T-cell lymphoma. *J Adv Pract Oncol*. 2015;6:22–36.

104. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist*. 2007;12:1247–1252. https://doi.org/10.1634/theoncologist.12-10-1247.

105. Hsieh Y-H, Su I-J, Yen C-J, et al. Histone deacetylase inhibitor suberoylanilide hydroxamic acid suppresses the pro-oncogenic effects induced by hepatitis B virus pre-S2 mutant oncoprotein and represents a potential chemopreventive agent in high-risk chronic HBV patients. *Carcinogenesis*. 2013;34:475–485. https://doi.org/10.1093/carcin/bgs365.

106. Tan S-L, ed. *Hepatitis C Viruses: Genomes and Molecular Biology*. Norfolk, UK: Horizon Bioscience; 2006.

107. Petruzzello A, Marigliano S, Loquercio G, Cozzolino A, Cacciauoti C. Global epidemiology of hepatitis C virus infection: an update of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol*. 2016;22:7824–7840. https://doi.org/10.3748/wjg.v22.i34.7824.

108. Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin Liver Dis*. 2005;9:383–398. vi https://doi.org/10.1016/j.cld.2005.05.003.

109. Blackard JT, Shata MT, Shire NJ, Sherman KE. Acute hepatitis C virus infection: a chronic problem. *Hepatology*. 2008;47:321–331. https://doi.org/10.1002/hep.21902.

110. Wong RJ, Gish RG. Metabolic manifestations and complications associated with chronic hepatitis C virus infection. *Gastroenterol Hepatol (N Y)*. 2016;12:293–299.

111. Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. *Ther Adv Infect Dis*. 2016;3:3–14. https://doi.org/10.1177/2049936115585942.

112. Zhang J, Nguyen D, Hu K-Q. Chronic hepatitis C virus infection: a review of current direct-acting antiviral treatment strategies. *N Am J Med Sci (Boston)*. 2016;9:47–54.

113. Lynch SM, Wu GY. Hepatitis C virus: a review of treatment guidelines, cost-effectiveness, and access to therapy. *J Clin Transl Hepatol*. 2016;4:310–319. https://doi.org/10.14218/JCTH.2016.00027.

114. Ampuero J, Romero-Gómez M, Reddy KR. Review article: HCV genotype 3—the new treatment challenge. *Aliment Pharmacol Ther*. 2014;39:686–698. https://doi.org/10.1111/apt.12646.

115. Hamdane N, Jühling F, Crouchet E, et al. HCV-induced epigenetic changes associated with liver cancer risk persist after sustained virologic response. *Gastroenterology*. 2019;156:2313–2329.e7. https://doi.org/10.1053/j.gastro.2019.02.038.

116. Feng Q, Hassan SA, Das T, Huang J, Feng Z, Gretch DR. Epigenetic mechanisms in hepatitis C virus-associated hepatocellular carcinoma: a potential new link between stem cells, virology and cancer. *Curr Res Med Sci*. 2013;4:21–35. https://doi.org/10.3844/amjsp.2013.21.35.

117. Ai T, Xu Y, Qiu L, Geraghty RJ, Chen L. Hydroxamic acids block replication of hepatitis C virus. *J Med Chem*. 2015;58:785–800. https://doi.org/10.1021/acs.jmedchem.5b00330g.

118. Gequelin LCF, Riediger IN, Nakatani SM, Biondo AW, Bonfim CM. Epstein–Barr virus: general factors, virus-related diseases and measurement of viral load after transplant. *Rev Bras Hematol Hemoter*. 2011;33:383–388. https://doi.org/10.5581/1516-8484.20110103.

119. Griffin BE. Epstein–Barr virus (EBV) and human disease: facts, opinions and problems. *Mutat Res*. 2000;462:395–405. https://doi.org/10.1016/s1383-5742(00)00028-4.

120. Hong Gk, Guley ML, Feng W-H, Delecouse H-J, Holley–Guthrie E, Kenney SC. Epstein–Barr virus lytic infection contributes to lymphoproliferative disease in a SCID mouse model. *J Virol*. 2005;79:13993–14003. https://doi.org/10.1128/JVI.79.22.13993-14003.2005.

121. Montone KT, Hodinka RL, Salhani KE, Lavi E, Rostami A, Tomaszewski JE. Identification of Epstein–Barr virus lytic activity in post-transplantation lymphoproliferative disease. *Mod Pathol*. 1996;9:621–630.

122. Young LS, Murray PG. Epstein–Barr virus and oncogenesis: from latent genes to tumours. *Oncogene*. 2003;22:5108–5121. https://doi.org/10.1038/sj.onc.1206556.
123. Tsai C-N, Tsai C-L, Tse K-P, Chang H-Y, Chang Y-S. The Epstein-Barr virus oncogene product, latent membrane protein 1, induces the downregulation of E-cadherin gene expression via activation of DNA methyltransferases. Proc Natl Acad Sci USA. 2002;99:10084–10089. https://doi.org/10.1073/pnas.152059399.

124. Anderton JA, Bose S, Vockerodt M, et al. The H3K27me3 demethylase, KDM6B, is induced by Epstein–Barr virus and over-expressed in Hodgkin’s lymphoma. Oncogene. 2011;30:2037–2043. https://doi.org/10.1038/onc.2010.579.

125. Cohen JI, Wang F, Mannick J, Kieff E. Epstein-Barr virus nuclear protein 2 is a key determinant of lymphocyte transformation. Proc Natl Acad Sci USA. 1989;86:9558–9562. https://doi.org/10.1073/pnas.86.23.9558.

126. Wang L, Grossman SR, Kieff E. Epstein–Barr virus nuclear protein 2 interacts with p300, CBP, and PCAF histone acetyltransferases in activation of the LMP1 promoter. Proc Natl Acad Sci USA. 2000;97:430–435.

127. Daigle D, Gradoville L, Tuck D, et al. Valproic acid antagonizes the capacity of other histone deace-tylase inhibitors to activate the Epstein–bar virus lytic cycle. J Virol. 2011;85:5628–5643. https://doi.org/10.1128/JVI.02659-10.

128. Ghosh SK, Perrine SP, Williams RM, Faller DV. Histone deacetylase inhibitors are potent inducers of gene expression in latent EBV and sensitize lymphoma cells to nucleoside antiviral agents. Blood. 2012;119:1008–1017. https://doi.org/10.1182/blood-2011-06-362434.

129. Sunil M, Reid E, Lechowicz MJ. Update on HHV–8–associated malignancies. Curr Infect Dis Rep. 2010;12:147–154. https://doi.org/10.1007/s11908-010-0092-5.

130. Shin HJ, DeCotiis J, Giron M, Palmeri D, Lukac DM. Histone deacetylase classes I and II regulate Kaposi’s sarcoma-associated herpesvirus reactivation. J Virol. 2014;88:1281–1292. https://doi.org/10.1128/JVI.02665-13.

131. Lechowicz M, Dittmer DP, Lee JY, et al. Molecular and clinical assessment in the treatment of AIDS Kaposi sarcoma with valproic acid. Clin Infect Dis. 2009;49:1946–1949. https://doi.org/10.1086/648447.

132. Wang H, Wang L, Erdjument-Bromage H, et al. Role of histone H2A ubiquitination in polycomb silencing. Nature. 2004;431:873–878. https://doi.org/10.1038/nature02985.

133. Grundhoff A, Ganem D. Inefficient establishment of KSHV latency suggests an additional role for continued lytic replication in Kaposi sarcoma pathogenesis. J Clin Invest. 2004;113:124–136. https://doi.org/10.1172/JCI17803.

134. Niedermeier A, Talanin N, Chung EJ, et al. Histone deacetylase inhibitors induce apoptosis with minimal viral reactivation in cells infected with Kaposi’s sarcoma-associated herpesvirus. J Invest Dermatol. 2006;126:2516–2524. https://doi.org/10.1038/sj.jid.5700438.

135. Braaten KP, Laufer MR. Human papillomavirus (HPV), HPV-related disease, and the HPV vaccine. Rev Obstet Gynecol. 2008;1:2–10.

136. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol. 2012;5:25–36.

137. Bansal A, Singh MP, Rai B. Human papillomavirus-associated cancers: a growing global problem. Int J Appl Basic Med Res. 2016;6:84–89. https://doi.org/10.4103/2229-516X.179027.

138. Center for Biologics Evaluation and Research. Human Papillomavirus Vaccine. FDA; 2018.

139. Stern PL, van der Burg SH, Hampson IN, et al. Therapy of human papillomavirus-related disease. Vaccine. 2012;30(suppl. 5):F71–F82. https://doi.org/10.1016/j.vaccine.2012.05.091.

140. Ward G, Mehta V, Moore M. Morbidity, mortality and cost from HPV-related oropharyngeal cancer: impact of 2-, 4- and 9-valent vaccines. Hum Vaccin Immunother. 2016;12(6):1343–1347. doi:10.1080/21645515.2015.1095415.

141. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016;4:e609–e616. https://doi.org/10.1016/S2214-109X(16)30143-7.

142. Yang S-H, Kong S-K, Lee S-H, Lim S-Y, Park C-Y. Human papillomavirus 18 as a poor prognostic factor in stage I-IIA cervical cancer following primary surgical treatment. Obstet Gynecol Sci. 2014;57:492–500. https://doi.org/10.5468/ogs.2014.57.6.492.
143. Byun JM, Jeong DH, Kim YN, et al. Persistent HPV-16 infection leads to recurrence of high-grade cervical intraepithelial neoplasia. *Medicine (Baltimore).* 2018;97. https://doi.org/10.1097/MD.00000000000013606.

144. Fuentes A. Advancements in cervical cancer prevention and management of persistent, recurrent, and metastatic disease: 2016 update. *Am J Hematol/Oncol.* 2017;12:8–17.

145. Durzynska J, Lesniewicz K, Koreba E. Human papillomaviruses in epigenetic regulations. *Mutar Rev Mutat Res.* 2017;772:36–50. https://doi.org/10.1016/j.mrrev.2016.09.006.

146. Plesa A, Iancu IV, Botezatu A, Huica I, Stoian M, Anton G. The involvement of epigenetic mechanisms in HPV-induced cervical cancer. In: *Human Papillomavirus—Research in a Global Perspective.* IntechOpen; 2016. https://doi.org/10.5772/62833.

147. Hyland PL, McDade SS, McCloskey R, et al. Evidence for alteration of EZH2, BMI1, and KDM6A and epigenetic reprogramming in human papillomavirus type 16 E6/E7-expressing keratinocytes. *J Virol.* 2011;85:10999–11006. https://doi.org/10.1128/JVI.00160-11.

148. Longworth MS, Wilson R, Laimins LA. HPV31 E7 facilitates replication by activating E2F2 transcription through its interaction with HDACs. *EMBO J.* 2005;24:1821–1830. https://doi.org/10.1038/sj.emboj.7600651.

149. Thomas MC, Chiang C-M. E6 oncoprotein represses p53-dependent gene activation via inhibition of protein acetylation independently of inducing p53 degradation. *Mol Cell.* 2005;17:251–264. https://doi.org/10.1016/j.molcel.2004.12.016.

150. de la Cruz-Hernández E, Pérez-Cárdenas E, Contreras-Paredes A, et al. The effects of DNA methylation and histone deacetylase inhibitors on human papillomavirus early gene expression in cervical cancer, an in vitro and clinical study. *Vir J.* 2007;4:18. https://doi.org/10.1186/1743-422X-4-18.

151. Song C, Zhu S, Wu C, Kang J. Histone deacetylase (HDAC) 10 suppresses cervical cancer metastasis through inhibition of matrix metalloproteinase (MMP) 2 and 9 expression. *J Biol Chem.* 2013;288:28021–28033. https://doi.org/10.1074/jbc.M113.498758.

152. Lien W-C, Chen T-Y, Sheu S-Y, et al. 7-hydroxy-staurosporine, UCN-01, induces DNA damage response, and autophagy in human osteosarcoma U2-OS cells. *J Cell Biochem.* 2018;119:4729–4741. https://doi.org/10.1002/jcb.26652.

153. Xie A-Y, Bermudez VP, Folk WR. Stimulation of DNA replication from the polyomavirus origin by PCAF and GCN5 acetyltransferases: acetylation of large T antigen. *Mol Cell Biol.* 2002;22:7907–7918. https://doi.org/10.1128/mcb.22.22.7907-7918.2002.

154. Dalianis T, Hirsch HH. Human polyomaviruses in disease and cancer. *Virology.* 2013;437:63–72. https://doi.org/10.1016/j.virol.2012.12.015.

155. Del Valle L, White MK, Khalili K. Potential mechanisms of the human polyomavirus JC in neural oncogenesis. *J Neuropathol Exp Neurol.* 2008;67:729–740. https://doi.org/10.1097/NEN.0b013e31818180e631.

156. Dahl J, Chen HI, George M, Benjamini TL. Polyomavirus small T antigen controls viral chromatin modifications through effects on kinetics of viral growth and cell cycle progression. *J Virol.* 2007;81:10064–10071. https://doi.org/10.1128/JVI.00821-07.

157. Bennett SM, Broekema NM, Imperiale MJ. BK polyomavirus: emerging pathogen. *Microbes Infect.* 2012;14:672–683. https://doi.org/10.1016/j.micinf.2012.02.002.

158. Fang C-Y, Shen C-H, Wang M, et al. Global profiling of histone modifications in the polyomavirus BK virion minichromosome. *Virology.* 2015;483:1–12. https://doi.org/10.1016/j.virology.2015.04.009.

159. Spurgeon ME, Lambert PF. Merkel cell polyomavirus: a newly discovered human virus with onco- genic potential. *Virology.* 2013;435:118–130. https://doi.org/10.1016/j.virology.2012.09.029.

160. Spurgeon ME, Lambert PF. Merkel cell polyomavirus: a newly discovered human virus with onco- genic potential. *Virology.* 2013;435:118–130. https://doi.org/10.1016/j.virology.2012.09.029.
163. Cheng J, Park DE, Berrios C, et al. Merkel cell polyomavirus recruits MYCL to the EP400 complex to promote oncogenesis. *PLoS Pathog.* 2017;13. https://doi.org/10.1371/journal.ppat.1006668.

164. Busam KJ, Pulitzer MP, Coit DC, et al. Reduced H3K27me3 expression in Merkel cell polyoma virus-positive tumors. *Mod Pathol.* 2017;30:877–883. https://doi.org/10.1038/modpathol.2017.8.

165. Gallo R.C. History of the discoveries of the first human retroviruses: HTLV-1 and HTLV-2. *Oncogene.* 2005;24:5926–5930. https://doi.org/10.1038/sj.onc.1208980.

166. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. *Mod Pathol.* 2017;30:877–883. https://doi.org/10.1038/modpathol.2017.8.

167. Panfil AR, Martinez MP, Ratner L, Green PL. Human T-cell leukemia virus-associated malignancy. *Curr Opin Virol.* 2016;20:40–46. https://doi.org/10.1016/j.coviro.2016.08.009.

168. Utsunomiya A, Choi I, Chihara D, Seto M. Recent advances in the treatment of adult T-cell leukemia-lymphomas. *Cancer Sci.* 2015;106:344–351. https://doi.org/10.1111/cas.12617.

169. Ohno N, Tani A, Uozumi K, et al. Expression of functional lung resistance—related protein predicts poor outcome in adult T-cell leukemia. *Blood.* 2001;98:1160–1165. https://doi.org/10.1182/blood.v98.4.1160.

170. Hermine O, Ramos JC, Tobinai K. A review of new findings in adult T-cell Leukemia—lymphoma: a focus on current and emerging treatment strategies. *Adv Ther.* 2018;35:135–152. https://doi.org/10.1007/s12325-018-0658-4.

171. Miyazato P, Matsuo M, Katsuya H, Satou Y. Transcriptional and epigenetic regulatory mechanisms affecting HTLV-1 provirus. *Viruses.* 2016;8:171. https://doi.org/10.3390/v8060171.

172. ClinicalTrials.gov (NCT01261247). Panobinostat in treating patients with relapsed or refractory non-Hodgkin lymphoma; 2010. https://clinicaltrials.gov/ct2/show/NCT01261247. Accessed 19 July 2019.

173. Stork L, Brück W, von Gottberg P, et al. Severe meningo-/encephalitis after daclizumab therapy for multiple sclerosis. *Mult Scler.* 2019;25:1618–1632. 1352458518819098, https://doi.org/10.1177/1352458518819098.

174. Mosley AJ, Meekings KN, McCarthy C, et al. Histone deacetylase inhibitors increase virus gene expression but decrease CD8+ cell antiviral function in HTLV-1 infection. *Blood.* 2006;108:3801–3807. https://doi.org/10.1182/blood-2006-03-013235.

175. Sellers SA, Hagan RS, Hayden FG, Fischer WA. The hidden burden of influenza: a review of the extrapulmonary complications of influenza infection. *Influenza Other Respir Viruses.* 2017;11:372–393. https://doi.org/10.1111/irv.12470.

176. Saunders-Hastings PR, Krewski D. Reviewing the history of pandemic influenza: understanding patterns of emergence and transmission. *Pathogens.* 2016;5:66. https://doi.org/10.3390/pathogens5040066.

177. van der Vries E, Schutten M, Fraaij P, Osterhaus A. Influenza virus resistance to antiviral therapy. *Adv Pharmacol.* 2013;67:217–246. https://doi.org/10.1016/B978-0-12-405880-4.00006-8.

178. Zhu W, Wang C, Wang B-Z. From variation of influenza viral proteins to vaccine development. *Int J Mol Sci.* 2017;18:1554. https://doi.org/10.3390/ijms18071554.

179. World Health Organization. *WHO fact sheet on influenza 2018.* https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). accessed July 19, 2019.

180. Putri WCWS, Muscatello DJ, Stockwell MS, Newall AT. Economic burden of seasonal influenza in the United States. *Vaccine.* 2018;36:3960–3966. https://doi.org/10.1016/j.vaccine.2018.05.057.

181. Hatakeyama D, Shoji M, Yamayoshi S, et al. Influenza A virus nucleoprotein is acetylated by histone acetyltransferases PCAF and GCN5. *J Biol Chem.* 2018;293:7126–7138. https://doi.org/10.1074/jbc.RA117.001683.

182. Nagesh PT, Husain M. Influenza A virus dysregulates host histone deacetylase 1 that inhibits viral infection in lung epithelial cells. *J Virol.* 2016;90:4614–4625. https://doi.org/10.1128/JVI.00126-16.

183. Chen L, Wang C, Luo J, et al. Histone deacetylase 1 plays an acetylation–independent role in influenza A virus replication. *Front Immunol.* 2017;8:1757. https://doi.org/10.3389/fimmu.2017.01757.

184. Chen H, Qian Y, Chen X, et al. HDAC6 restricts influenza A virus by deacetylation of the RNA polymerase PA subunit. *J Virol.* 2019;93. https://doi.org/10.1128/JVI.01896-18 01896-18.

185. Husain M, Cheung C-Y. Histone deacetylase 6 inhibits influenza A virus release by downregulating the trafficking of viral components to the plasma membrane via its substrate, acetylated microtubules. *J Virol.* 2014;88:11229–11239. https://doi.org/10.1128/JVI.00727-14.
186. Husain M, Harrod KS. Influenza a virus-induced caspase-3 cleaves the histone deacetylase 6 in infected epithelial cells. FEBS Lett. 2009;583:2517–2520. https://doi.org/10.1016/j.febslet.2009.07.005.

187. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23. https://doi.org/10.1007/978-1-4939-2438-7_1.

188. Bailey OT, Pappenheimer AM, Cheever FS, Daniels JB. A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin: II. Pathology. J Exp Med. 1949;90:195–212. https://doi.org/10.1084/jem.90.3.195.

189. Mers-Cov Research Group. State of knowledge and data gaps of Middle East respiratory syndrome coronavirus (MERS-CoV) in humans. PLoS Curr. 2013;5. https://doi.org/10.1371/currents.outbreaks.0bf719e352e7478fad85fa30127db8.

190. Menachery VD, Baric RS. Epigenetic landscape during coronavirus infection. Pathogens. 2017;6:8. https://doi.org/10.3390/pathogens6010008.

191. Menachery VD, Burnum-Johnson KE, et al. Pathogenic influenza viruses and coronaviruses utilize similar and contrasting approaches to control interferon-stimulated gene responses. MBio. 2014;5. https://doi.org/10.1128/mBio.01174-14.

192. Menachery VD, Schäfer A, Burnum-Johnson KE, et al. MERS-CoV and H5N1 influenza virus antagonize antigen presentation by altering the epigenetic landscape. Proc Natl Acad Sci USA. 2018;115:E1012–E1021. https://doi.org/10.1073/pnas.1706928115.

193. Gould E, Pettersson J, Higgs S, Charrel R, de Lamballerie X. Emerging arboviruses: why today? One Health. 2017;4:1–13. https://doi.org/10.1016/j.onehlt.2017.06.001.

194. Huang Y-JS, Higgs S, Vanlandingham DL. Emergence and re-emergence of mosquito–borne arboviruses. Curr Opin Virol. 2019;34:104–109. https://doi.org/10.1016/j.coviro.2019.01.001.

195. de Aguiar GPCG, da Leite CMGS, Dias B, et al. Evidence for host epigenetic signatures arising from arbovirus infections: a systematic review. Front Immunol. 2019;10:1207. https://doi.org/10.3389/fimmu.2019.01207.

196. Devhare P, Meyer K, Steele R, Ray RB, Ray R. Zika virus infection dysregulates human neural stem cell growth and inhibits differentiation into neuroprogenitor cells. Cell Death Dis. 2017;8 https://doi.org/10.1038/cddis.2017.517.

197. Colpitts TM, Barthel S, Wang P, Fikrig E. Dengue virus capsid protein binds core histones and inhibits nucleosome formation in human liver cells. PLoS One. 2011;6. https://doi.org/10.1371/journal.pone.0024365.

198. Tarakhovsky A, Prinjha RK. Drawing on disorder: how viruses use histone mimicry to their advantage. J Exp Med. 2018;215:1777–1787. https://doi.org/10.1084/jem.20180099.

199. Center for Disease Control and Prevention. Years of Ebola Virus Disease Outbreaks 2019. https://www.cdc.gov/vhf/ebola/history/chronology.html. accessed July 19, 2019.

200. Kaner J, Schaack S. Understanding Ebola: the 2014 epidemic. Glob Health. 2016;12:53. https://doi.org/10.1186/s12992-016-0194-4.

201. Falasca L, Agrati C, Petrosillo N, et al. Molecular mechanisms of Ebola virus pathogenesis: focus on cell death. Cell Death Differ. 2015;22:1250–1259. https://doi.org/10.1038/cdd.2015.67.

202. Mühlberger E, Weik M, Volchkov VE, Klenk HD, Becker S. Comparison of the transcription and replication strategies of Marburg virus and Ebola virus by using artificial replication systems. J Virol. 1999;73:2333–2342.

203. Huang Y, Xu L, Sun Y, Nabel GJ. The assembly of Ebola virus nucleocapsid requires virion–associated proteins 35 and 24 and posttranslational modification of nucleoprotein. Mol Cell. 2002;10:307–316.

204. Hatakeyama D, Ohmi N, Saitoh A, et al. Acetylation of lysine residues in the recombinant nucleoprotein and VP40 matrix protein of Zaire Ebolavirus by eukaryotic histone acetyltransferases. Biochem Biophys Res Commun. 2018;504:635–640. https://doi.org/10.1016/j.bbrc.2018.09.007.

205. Proserpio V, Fittipaldi R, Ryall JG, Sartorelli V, Caretti G. The methyltransferase SMYD3 mediates the recruitment of transcriptional cofactors at the myostatin and c-Met genes and regulates skeletal muscle atrophy. Genes Dev. 2013;27:1299–1312. https://doi.org/10.1101/gad.217240.113.

206. García-Dorival I, Wu W, Armstrong SD, et al. Elucidation of the cellular Interactome of Ebola virus nucleoprotein and identification of therapeutic targets. J Proteome Res. 2016;15:4290–4303. https://doi.org/10.1021/acs.jproteome.6b00337.
207. Biedenkopf N, Hartlieb B, Hoenen T, Becker S. Phosphorylation of Ebola virus VP30 influences the composition of the viral nucleocapsid complex: impact on viral transcription and replication. J Biol Chem. 2013;288:11165–11174. https://doi.org/10.1074/jbc.M113.461285.

208. Chang T-H, Kubota T, Matsuoka M, et al. Ebola Zaire virus blocks type I interferon production by exploiting the host SUMO modification machinery. PLoS Pathog. 2009;5. https://doi.org/10.1371/journal.ppat.1000493.

209. Teng Y, Wang Y, Zhang X, et al. Systematic genome-wide screening and prediction of microRNAs in EBOV during the 2014 ebolavirus outbreak. Sci Rep. 2015;5:9912. https://doi.org/10.1038/srep09912.

210. Kohno T, Goto T, Takasaki T, et al. Fine structure and morphogenesis of Borna disease virus. J Virol. 1999;73:760–766.

211. Carbone KM. Borna disease virus and human disease. Clin Microbiol Rev. 2001;14:513–527. https://doi.org/10.1128/CMR.14.3.513–527.2001.

212. Lipkin WI, Briese T, Hornig M. Borna disease virus—fact and fantasy. Virus Res. 2011;162:162–172. https://doi.org/10.1016/j.virusres.2011.09.036.

213. Gosztonyi G, Ludwig H. Borna disease—neuropathology and pathogenesis. Curr Top Microbiol Immunol. 1995;190:39–73.

214. Sierra-Honigmann AM, Rubin SA, Estafanous MG, Yolken RH, Carbone KM. Borna disease virus in peripheral blood mononuclear and bone marrow cells of neonatally and chronically infected rats. J Neuroimmunol. 1993;45:31–36.

215. Matsumoto Y, Hayashi Y, Omori H, et al. Bornavirus closely associates and segregates with host chromosomes to ensure persistent intranuclear infection. Cell Host Microbe. 2012;11:492–503. https://doi.org/10.1016/j.chom.2012.04.009.

216. Suberbielle E, Stella A, Pont F, et al. Proteomic analysis reveals selective impediment of neuronal remodeling upon Borna disease virus infection. J Virol. 2008;82:12265–12279. https://doi.org/10.1128/JVI.01615-08.

217. Liu X, Zhao L, Yang Y, et al. Human borna disease virus infection impacts host proteome and histone lysine acetylation in human oligodendroglia cells. Virology. 2014;464–465:196–205. https://doi.org/10.1016/j.virol.2014.06.040.

218. Liu X, Liu S, Bode L, et al. Persistent human Borna disease virus infection modifies the acetylome of human oligodendroglia cells towards higher energy and transporter levels. Virology. 2015;485:58–78. https://doi.org/10.1016/j.virol.2015.06.024.

219. Bonnaud EM, Szélechowski M, Bétourné A, et al. Borna disease virus phosphoprotein modulates epigenetic signaling in neurons to control viral replication. J Virol. 2015;89:5996–6008. https://doi.org/10.1128/JVI.00454-15.

220. Carbone J. The immunology of posttransplant CMV infection: potential effect of CMV immunoglobulins on distinct components of the immune response to CMV. Transplantation. 2016;100:S11. https://doi.org/10.1097/TP.0000000000001095.

221. Zhou L, He X, Gao B, Xiong S. Inhibition of histone deacetylase activity aggravates coxsackievirus B3-induced myocarditis by promoting viral replication and myocardial apoptosis. J Virol. 2015;89:10512–10523. https://doi.org/10.1128/JVI.01028-15.