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CHAPTER 10

Targeting histone epigenetics to control viral infections

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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.[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.[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.[10] Cellular host factors recruit HDACs to HIV-1 5'LTR, resulting in the repression of the HIV-1-associated nucleosome nuc-1.[11] HMTs also induce the silencing of proviral DNA by changing the methylation state of histone H3, resulting in the condensation of nuc-1.[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).[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).[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.[11,13] HDAC inhibitors were first tested in cancer research,

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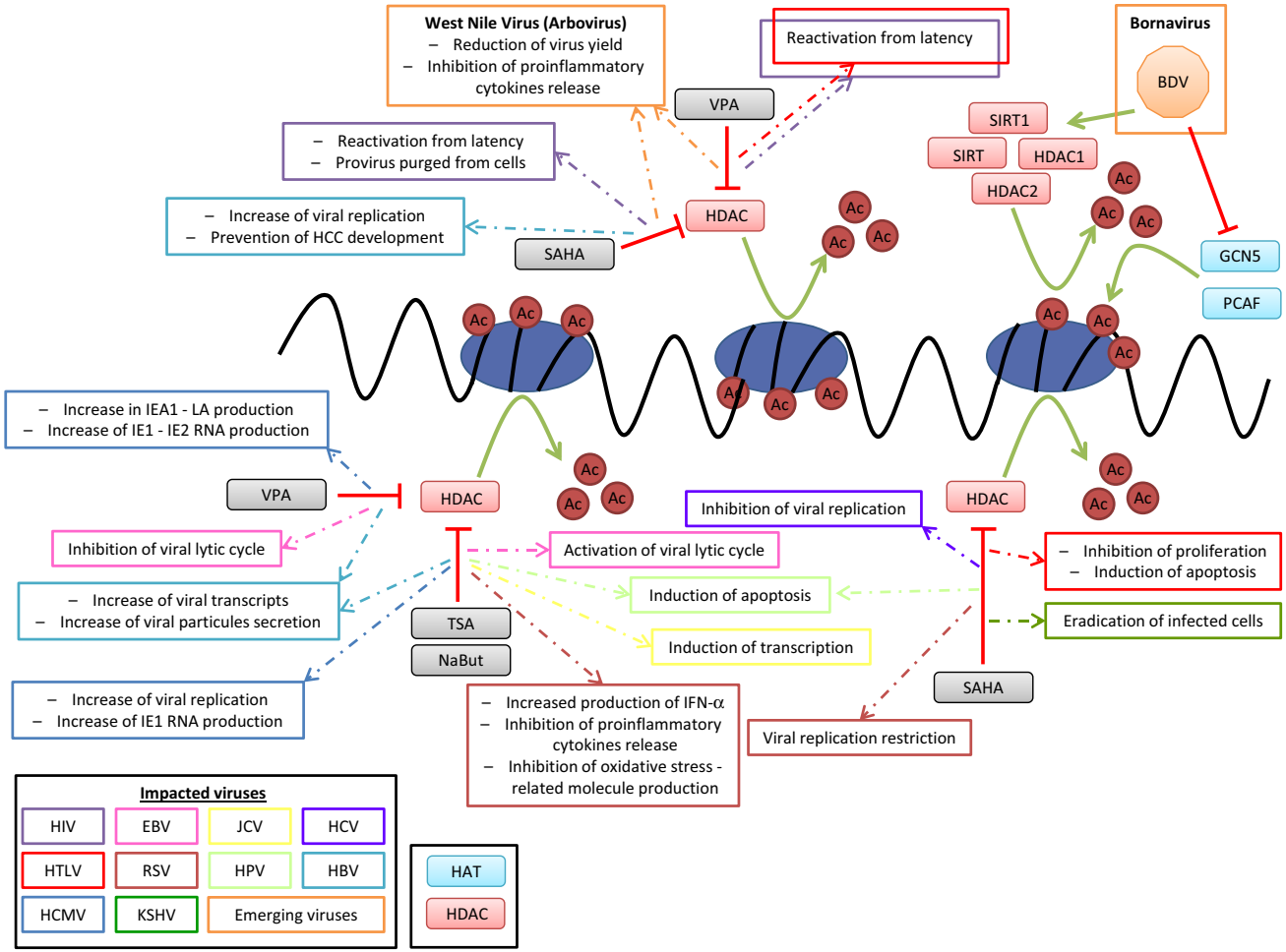

Fig. 10.1 Targeting histone acetylation in the management of chronic viral infections (HIV, HCMV, RSV), virus-induced cancers (EBV, HCV, HTLV, HPV, HBV, KSHV), and epidemic/emerging viruses (WNV, BDV).

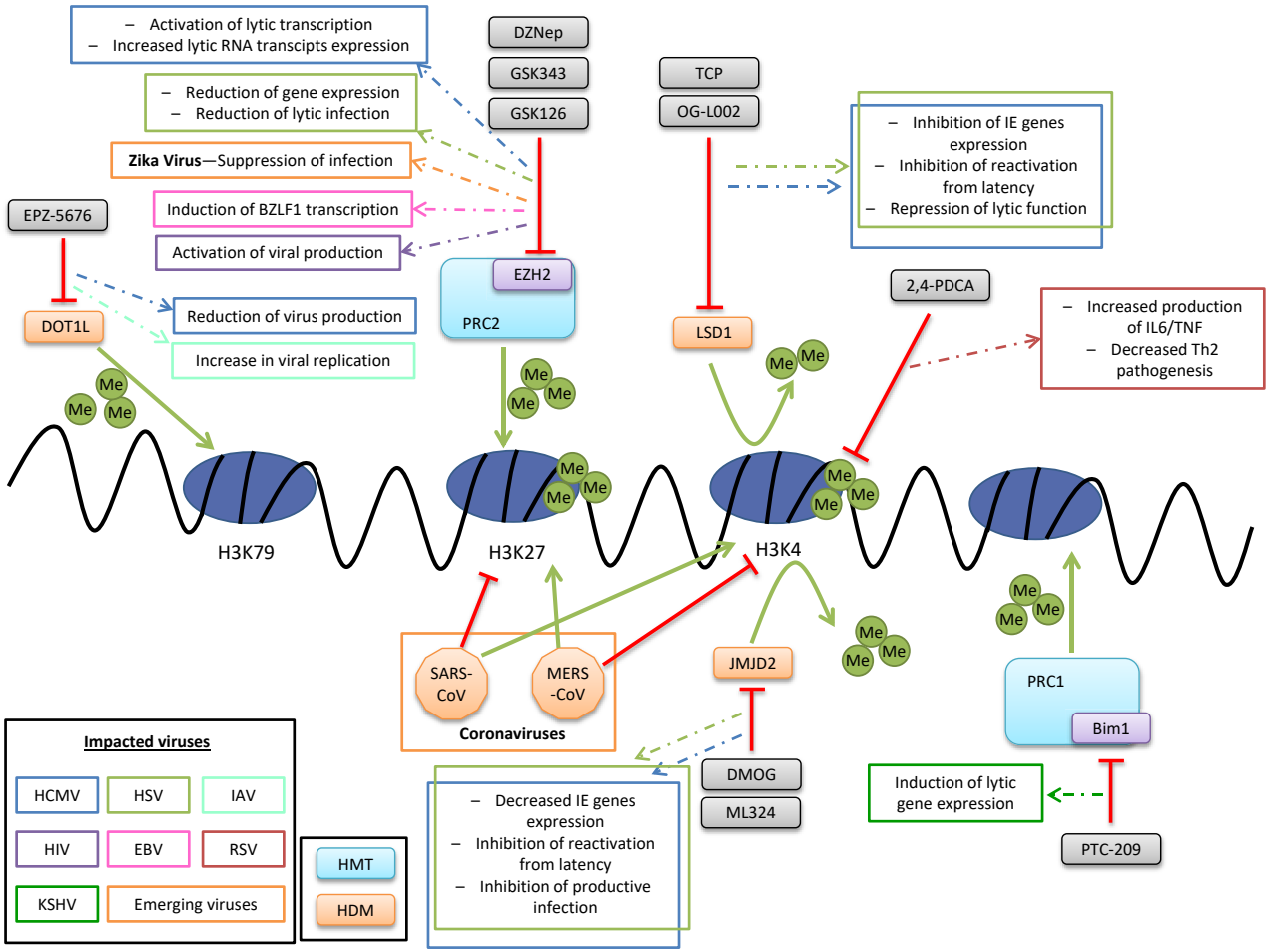

Fig. 10.2 Targeting histone methylation in the management of chronic viral infections (HIV, HSV, HCMV, RSV), virus-induced cancers (EBV, KHSV), and epidemic/emerging viruses (IAV, ZIKV, SARS-CoV, MERS-CoV).

where they showed a low toxic profile and an absence of T cell activation.[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.[44] Interestingly, treatment with HDAC inhibitor romidepsin was reported to prevent de novo infection of CD4 + T cells.[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.[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.[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.[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.[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 is an episomal form, along with repression of viral lytic genes expression, a state known as latency.[67] Occasionally, and in response to various stimuli, the latent virus could be reactivated where lytic infection and production of infectious particles are resumed.[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.[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

Table 10.1 Functional outcomes of histone acetylation regulation in viral infections.

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]
			DENV	Reduction in the secretion of inflammatory cytokines[20]
			WNV	Inhibition of complete viral yield[21]
	Pan-HDAC	Trichostatin A (TSA)	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]
			JCV	Stimulation of early and late transcription[28]
	Pan-HDAC	Vorinistat/ suberanilohydroxamic acid (SAHA)	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]

Continued

Table 10.1 Functional outcomes of histone acetylation regulation in viral infections—cont'd

Target class	Target	Inhibitor	Virus studied	Functional outcome
			HBV	Stimulation of HBV replication[29]
			HCV	Inhibition 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]
			BDV	Counteracting the damaging effects of BDV-1 on synaptic plasticity[34]
	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]
	Pan-HDAC	Phenylbutyrate (PB)	HPV	Inhibition of cervical carcinoma cell growth[35]
	Pan-HDAC	TCA	HCV	Inhibition of HCV replication[30]
	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	HTLV-1	Inhibition of tumor growth and survival prolongation in a murine model of human ATL[37]

Combination	HDAC inhibitor + HMT inhibitor	TSA + DZNep	EBV	Induction of BZLF1 transcription[38]
	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[53]
HMT	Suv39H	Chaetocin	EBV	Transactivation of BZLF1 gene in B95-8 cells but not in Akata or Raji cells[54]
			HIV	Reversal of HIV-1 latency in model cell lines and cells derived from patients[11]
	G9a	BIX-01294	HIV	Reversal of HIV-1 latency in model cell lines and cells derived from patients[11]
	EZH2	GSK126	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[55]
			ZIKV	Suppression of infection[55]
		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[55]
			HCMV	Stimulation of significant increases in the lytic RNA transcript expression[56]
		UNC1999	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[55]
		DZNep	HIV	Reversal of HIV-1 latency in model cell lines and cells derived from patients[11]
			HCMV	Induction of activation of the lytic transcription program in two cellular models of HCMV quiescence[56]
			HPV	Antiproliferative characteristics in HPV-positive oropharyngeal squamous cell carcinomas[57]
	DOT1L	EPZ-5676	IVA	Increase in viral replication[58]

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[59]
			HCMV	Repression of the expression of HCMV IE genes[59]
		TCP	HSV-1	Suppression of lytic infection in a mouse model of neonatal infection and a rabbit eye model of herpetic keratitis plus a reduction in viral reactivation and shedding, as well as lesion recurrence in a guinea pig vaginal model[60]
			HCMV	Repression of the expression of HCMV IE genes[61]
	KDM4	DMOG	HSV-1	Block of the initiation of viral productive infection and reactivation in the sensory ganglia of latently infected mice[61]
			HCMV	Decrease in the expression of the UL37, UL72, and US3 HCMV genes[61]
		ML324	HSV-1	Seventy-five-fold more efficiency in suppressing infection than DMOG[61]
	KDM5B	2,4-PDCA	RSV	Increase in the production of proinflammatory cytokines and decrease in Th2 pathogenesis in vivo[62]
Polycomb repressive complex 1	Bim1	PTC-209	KSHV	Induction of KSHV lytic gene expression[63]
Combination	HDM inhibitor + DNA polymerase inhibitor	TCP + acyclovir	HSV-1	Increase in survival of infected mouse[60]

infection or reactivation from latency.[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.[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.[60] As LSD1 removes mono- and dimethylation marks,[71] the activity of another demethylase, JMJD2, is indispensable to remove trimethylation.[72] It has been shown that the use of dimethyloxalylglycine (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.[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.[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.[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.

10.1.3 Human cytomegalovirus (HCMV)

Another member of the Herpesviridae family is the human cytomegalovirus or, alternatively, the human herpes virus 5 (HHV-5).[74] Although HCMV affects 40%–99% of the population,[75] 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.[76] 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.[77] 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.[78,79] 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.[80,81] In this regard and in parallel to HSV infection, the LSD1 inhibitors OG-L002 or TCP significantly repressed the expression of HCMV IE genes,[59,61] and the JMJD2 inhibitor DMOG decreased the expression of the UL37, UL72, and US3 HCMV genes with a more potent inhibition noted with the use of ML324.[61] 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).[82] 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).[83–85] 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.[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, BMI 1 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.[86] On the other hand, a dynamic acetylation-deacetylation pattern of HCMV chromatin is noted during various stages of the infectious cycle.[87] In fact, histone deacetylases (HDACs) are known to play a role in the repression of viral replication.[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).[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.[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).[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.[89,90] Not limited to children, this pathogen is increasingly identified as a cause of illness in elderly and high-risk adults.[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-α (IFNα)-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).[24] 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).[62] 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.[92] 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.[93] 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).[94] Despite the introduction of FDA-approved antiviral drugs exemplified mainly by nucleos(t)ide analogues and pegylated interferon-α and expanded immunization,[95] the number of individuals with chronic HBV infection is estimated to be 240 million,[96] 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.[97] 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.[98] 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 lymphoma[103] and SAHA for advanced primary cutaneous T-cell lymphoma[104]), 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,

immunologic responses, and many others.[109] 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.[110,111] 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.[112] 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.[113] In addition, although oral antiviral regimens cover all HVC genotypes, treatment of patients with the second most prevalent genotype 3 (GT 3),[107] who are at a higher risk of developing HCC, is highly challenging as interferon-free treatment options are suboptimal.[114] Given the epigenetic alterations associated with HCV infection and its link to HCC,[115,116] 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.[30] However, another study pointed toward significant cytotoxicity at a low molar concentration of SAHA treatment despite its anti-HCV activity.[117] 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.[31] 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).[36] 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.[118] 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.[119] 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.[120,121] In contrast, it has been established that several viral latency proteins are unquestionably necessary for the oncogenic transformation.[122] 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.[123] Furthermore, LMP1 transcriptionally upregulates the histone demethylase KDM6B, which may contribute to the pathogenesis of HL.[124] Epstein–Barr virus (EBV) nuclear protein 2 (EBNA2), a key determinant of primary B lymphocyte growth transformation,[125] was shown to alter histone acetylation by interaction with p300/CBP complex to activate transcription.[126] 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 deacetylation inhibition that is essential to disrupt EBV latency (Fig. 10.1).[25] 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.[38] 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 (Fig. 10.2).[54] 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.[127] 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".[128] 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.[129] Based on sequence homology, KSHV shares several properties with EBV.[25] 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[63,130] and in vivo (Fig. 10.1).[131] 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),[132] also induced KSHV lytic gene expression in PEL cells (Fig. 10.2).[63] It is noteworthy that since lytic proteins contribute to KSHV-mediated oncogenesis,[133] 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 KHSH 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.[39] 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.[134]

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.[135] While LR HPV is responsible of 90% of anogenital condyloma or genital warts,[136] the persistent infection by HR HPV has the potential to advance into high-grade dysplasia and neoplastic transformation, including cervical, anogenital, and oropharyngeal cancers.[137] In fact, the introduction of three FDA-approved HPV

vaccines[138] and the availability of various therapeutic options[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[140] as the pathogen remains a main causative player of infection-related cancer in both men and women.[141] For instance, HPV-18 is considered a poor prognostic factor in stage I–IIA cervical cancer following primary surgical treatment,[142] and persistent HPV-16 infection is correlated to the recurrence of high-grade cervical intraepithelial neoplasia.[143] Knowing that advanced, recurrent, or metastatic cervical cancer share poor prognosis[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.[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.[147] E7 protein in HPV-31 binds to and inhibits HDACs, thus enhancing viral replication by activating E2F2 transcription.[148] E6 oncoprotein inhibits p300-mediated acetylation on p53 and nucleosomal core histones, which mediates repression of p53 transactivation.[149] Hence, targeting some members of the epigenetic machinery could play a role in controlling HPV infection and/or HPV-preneoplastic 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.[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.[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.[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).[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.[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.[151] 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.[40] Similarly, sodium butyrate, in combination with 7-hydroxy-staurosporine (UCN-01), a protein kinase C inhibitor with a potential antitumor spectrum,[152] enhanced intrinsic apoptotic pathways in HPV-positive human cervical carcinoma cells through p53 and p73 signaling and inhibited tumor growth in xenografted nude mice.[41] 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.[153] 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.[57] 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.[154] 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.[1,6] 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.[155] 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.[156] 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).[157] 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.[158] 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 oncogenic 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.[165] With five to ten million HTLV-1-infected individuals,[166] 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).[167] 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.[168] For instance, intensive chemotherapy has very limited benefit in aggressive ATL.[169] In addition, treatment options and outcomes in the setting of relapsed or primary refractory ATL represent a specific challenge and are generally unsatisfactory.[170] 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,[171] 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.[33] 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.[172] 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.[37] The use of daclizumab was stopped in 2018 due to side effects such as encephalitis and meningoencephalitis.[173] 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).[17] 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.[18] 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.[19] 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.[174] 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.[175] 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.[176] What adds a layer of complexity is the emergence of virus mutations that could precipitate resistance to the antiviral therapy, rendering it ineffective.[177] In addition, current IAV vaccines induce only short-term seasonal immunity and no universal IAV vaccine is available.[178] 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.[179] 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.[180] 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).[58] 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.[181] In addition, HDAC1 is demonstrated to inhibit IAV infection by being a vital part of host type I interferon (IFN)-mediated response against IAV.[182] 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.[183] 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.[184] Moreover, HDAC6 exhibited an anti-IAV activity by negatively regulating the trafficking of viral components to the site of virus assembly.[185] 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.[186] 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.[187] 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.[188] 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.[187,189] 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.[190] 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.[191] 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.[192] 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.[193] What adds a layer of complexity is lack of effective definitive treatment, although multiple vaccine candidates have shown promise for DENV.[194] 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.[195] 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).[55] 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.[196] 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.[20] 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.[197] 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.[198] 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.[21] 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).[43] 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.[199] 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.[200] Belonging to the *Filoviridae* family, EBOV is a single-stranded negative-sense RNA virus that encodes at least eight distinct proteins.[201] 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[202] and nucleocapsid formation, respectively,[203] are acetylated in their functional domains by eukaryotic HATs, including P300/CREB-binding protein (P300/CBP) and P300/CBP-associated factor (PCAF), in vitro.[204] Interestingly, SMYD3, a histone-lysine *N*-methyltransferase that plays a vital role in transcriptional activation by being a member of the RNA polymerase complex,[205] was recognized to interact with Ebolavirus NP, suggesting its potential role in modulation of the transcriptional activity of vRNA and mRNA.[206] It should

be noted that an interplay exists between EBOV proteins and various posttranslational modifications: VP30 phosphorylation modulates both viral transcription and replication,[207] VP35 blocks IFN production in innate immune cells by exploiting the host SUMO modification machinery,[208] 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.[209] However, those modifications will not be discussed here since this it 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,[210,211] although its ability to infect humans is still a matter of controversy.[212] In fact, BDV replicates and persists in the cellular compartment of the nervous system, comprising neurons, astrocytes, and oligodendrocytes,[213] in addition to nonneural cells, namely, peripheral blood mononuclear and bone marrow cells.[214] 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.[215,216] 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).[217] 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.[218] 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.[219] 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.[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.[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.[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.

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