Review

Epigenetic modulation of host: new insights into immune evasion by viruses

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Viruses have evolved with their hosts, which include all living species. This has been partly responsible for the development of highly advanced immune systems in the hosts. However, viruses too have evolved ways to regulate and evade the host's immune defence. In addition to mutational mechanisms that viruses employ to mimic the host genome and undergo latency to evade the host's recognition of the pathogen, they have also developed epigenetic mechanisms by which they can render the host's immune responses inactive to their antigens. The epigenetic regulation of gene expression is intrinsically active inside the host and is involved in regulating gene expression and cellular differentiation. Viral immune evasion strategies are an area of major concern in modern biomedical research. Immune evasion strategies may involve interference with the host antigen presentation machinery or host immune gene expression capabilities, and viruses, in these manners, introduce and propagate infection. The aim of this review is to elucidate the various epigenetic changes that viruses are capable of bringing about in their host in order to enhance their own survivability and pathogenesis.

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1. Introduction

Genes for a given trait are passed down to progeny from both parents in accordance with Mendelian inheritance. However, these genes are epigenetically marked before transmission, which alters their levels of expression. Such a phenomemon, called *genomic imprinting*, takes place before gamete formation and is erased during the formation of germ line cells. Genomic imprinting is an epigenetic phenomenon. Epigenetics entail the inducible genetic changes in an organism in which both adaptiveness and specificity may be very high. Epigenetic changes signify those changes in the gene expression of organisms which are global in nature and can be induced through a common or more universal system. The most common mechanisms that produce epigenetic changes are DNA methylation and histone acetylation.

Viruses have co-evolved with their hosts, which has given them the unique ability to adjust and exploit the host system for their propagation. They have evolved distinctive strategies to repress host immune response genes through epigenetic regulation of immune gene clusters. In the following sections are described various epigenetic apparatus that are normally present in the host, and how they can be manipulated by pathogenic organisms for their propagation. This review is an attempt to provide a holistic and comparative view of a relatively nascent

Keywords. Epigenetic modulation; histone deacetylases; HDAC inhibitors; immune evasion; methyl-binding domains

Abbreviations used: aza-CdR, 5-aza-2 deoxycytidine; BL, Burkitt's lymphoma; CBF-1, CSL family protein; CBP, CREB-protein-binding protein; CREB, cAMP-response-element-binding; CD4, cluster of differentiation 4; EBNA3C, Epstein–Barr virus nuclear antigen 3C; H3K9, histone H3 lysine 9; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; HMT, histone methyltransferase; ICP, infected cell polypeptide; JAK, janus kinase; PUMA, p53 up-regulated modulator of apoptosis; MBD, methyl-CpG-binding domain; MeCP2, methyl CpG binding protein 2; MICB, MHC class I chain-related protein B; NPC, naspharyngeal carcinoma; NuRD, nucleosome remodeling and deacetylase; ORF66p, open reading frame 66 protein kinase; PGDF, platelet-derived growth factor; PUMA, p53 up-regulated modulator of apoptosis; SAHA, suberyolanilide hydroxamc acid; STAT, signal transducers and activator of transcription; T Ag, large T antigen; TK, thymidine kinase

area of research and to clarify the ambiguities associated with pathogenic immune evasion mechanisms related to epigenetic alterations.

2. Role of epigenetics in regulation of gene expression

Epigenetic control of gene expression is complex and consists of multiple facets, including histone modification, miRNA pathways and DNA methylation. Histone acetylation and DNA methylation are the main mechanisms of epigenetic regulation (Zocchi and Sassone-Corsi 2010). The miRNA pathway is usually activated during cancer or viral infection. A detailed description of the role of miRNA in gene regulation has been provided in a later section.

2.1 *Histone modifications*

The extent of acetylation of core histones reflects a balance between the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs) (figure 1). In the deacetylated state, histones package the DNA into condensed chromatin, termed *nucleosomes*, which, in turn, prevent access of transcriptional activators to their target sites, thus resulting in transcriptional repression. Relaxation of the nucleosomes occur by the acetylation of the conserved N-terminal histone tails, which decrease the interaction of the positively charged histone tails with the negatively charged phosphate backbone of DNA. The nucleosomal relaxation facilitates access of transcriptional activators and allows gene expression. Furthermore, many transcriptional co-activators such as p300 and CBP (CRE-binding protein, where CRE is cAMP-response-element-binding protein) display intrinsic HAT activity, which reinforces chromatin relaxation.

Hypoacetylated histones are associated with transcriptionally silent genes, which is consistent with the discovery that HDACs are present in the same complex along with other transcriptional repressors. There are four groups of HDAC proteins classified according to function and DNA sequence similarity. The first two groups are considered to be Zn^{2+}-dependent "classical" HDACs whose activities are inhibited by Trichostatin A (TSA), whereas the third group is a family of NAD^{+}-dependent proteins not affected by TSA. The fourth group is considered an atypical category of its own, based solely on DNA sequence similarity with the others. Class I HDACs (HDACs 1, 2, 3 and 8) are localized in the nucleus and are present as multi-protein complexes. They are not DNA-binding proteins. HDACs located in the nucleus show maximum deacetylase activity. They have ubiquitous expression and play key roles in normal cells. Class II HDAC (HDACs 4, 5, 7, 9, 6 and 10) expression is tissue-specific and can shuttle between the nucleus and cytoplasm (de Ruijter *et al.* 2003). This class of HDACs has lower deacetylase activity than their class I counterparts. The functions of class I and class II HDACs in epigenetic regulation of gene expression have been well-elucidated. Class IIb HDACs (HDAC6 and HDAC10) contain two deacetylase domains and are capable of deacetylating cytoplasmic proteins to modulate their activity (Duong *et al.* 2008). Class III HDACs (the sirtuins) show anti-oxidant properties, while functionally there is much to be studied as far as class IV HDACs (potentially, HDAC11) are concerned (Wang *et al.* 2009).

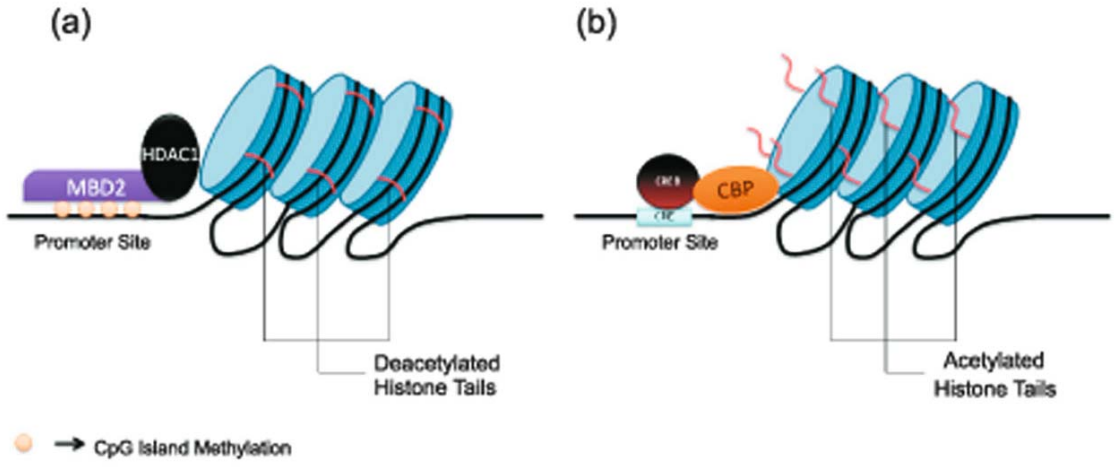

Figure 1. Epigenetic regulation of gene expression: **(a)** Inhibition: HDACs deacetylate histone tails, which clamp onto genome around nucleosome, thus inhibiting transcription. Methyl-binding proteins (e.g. MBDs) bind to methylated CpG islands in the promoter site of DNA and form an inhibitory complex with HDACs and other co-inhibitory molecules (not shown) to further strengthen inhibition. **(b)** Activation: histone acetylases such as CBP acetylate histone tails to unclamp DNA and allow unwinding. CBP also acts as a co-activator along with CREB, which bind to promoter sequences to initiate transcription.

2.2 *DNA methylation*

Methylation at CpG dinucleotides in genomic DNA is another fundamental epigenetic mechanism of gene expression control in vertebrates. Proteins with a methyl-CpG-binding domain (MBDs) can bind to single methylated CpGs and most of them are involved in transcriptional control (Bird 1996; Roloff *et al.* 2003). So far, five vertebrate MBDs have been described as MBD family members: MBD1, MBD2, MBD3, MBD4 and MeCP2 (Ballestar and Wolffe 2001; Wade 2001). Strong evidence exists for the correlation between DNA hypermethylation, hypoacetylation of histones, tightly packed chromatin and transcriptional repression. Except for MBD4, all other members of the MBD family are associated with HDACs, and a transcriptional repression mechanism mediated by the recruitment of HDACs has been shown for MeCP2, MBD1 and MBD2 (Ohki *et al.* 1999).

3. Aspects of non-epigenetic viral immune evasion: prominence of mimicry

Viruses can exist in two forms: as extracellular virion particles or as intracellular genomes. While the former is resistant to physical stress, the latter is more susceptible to the humoral immune control. Various mechanisms of immune evasion are devised to protect viral genome and enhance their replication capabilities. Viral immunoregulatory proteins may be encoded as genes either with or without sequence homology with host genes. Large DNA viruses such as herpesvirus encode viral homologs derived from mutated host genes. On the other hand, certain viral immunoregulatory genes do not bear a sequence similarity to host genes, and may reflect a model of viral co-evolution with host through selection pressure (Alcami and Koszinowski 2000).

At the antigen presentation level, major histocompatibility complex (MHC) gene products are important factors in intercellular recognition and self- and non-self-discrimination. The various host-mimicking proteins of the virus interfere with antigen-binding properties of MHC molecules. Epstein–Barr virus EBNA1 protein is capable of blocking antigen-processing while the herpes simplex virus ICP47 protein hinders transporters associated with antigen processing (TAP) activity. Viruses can modify maturation, assembly and export of MHC class I molecules. They are able to downregulate MHC class I molecules while hindering MHC class II functions (Farrell and Davis-Poynter 1998).

At the level of anti-viral responses, viruses are able to block interferon (IFN)-induced transcriptional responses and JAK/STAT signalling pathways. Critical members of the IFN effecter pathway such as the dsRNA-dependant protein kinase (PKR) can be inhibited by vaccinia virus (Smith *et al.* 1997). Eukaryotic translation initiation factor 2α (eIF-2α) and RNase L system can be inhibited by the herpes simplex virus and the vaccinia virus respectively (Goodbourn *et al.* 2000). Poxviruses encode soluble homologs of IFN-α, IFN-β and IFN-γ receptors capable of binding to host interferons and inactivating them. Synthesis of interferons can also be blocked by several viruses (Spriggs 1996).

The African swine fever virus (ASFV) replicates in macrophages and encodes an IκB homolog that blocks nuclear factor NFκB and nuclear-factor-activated T-cell (NFAT) mediated cytokine expression (Miskin *et al.* 1998). Certain viruses encode ligands for the tumour necrosis factor (TNF) family of receptors. Epstein–Barr virus (EBV) latent membrane protein 1 (LMP1) recruits components of the TNF receptor (TNFR) and CD40 to activate selective cytokine responses that could be beneficial for the virus, such as enhancing cell proliferation (Farrell 1998). Occupying the ranks of cytokine/chemokine modulation are the production of "virokines" and "viroreceptors", the viral homologs of cytokines and cytokine receptors. While virokines induce signalling pathways promoting virus replication, the viroreceptors neutralize host cytokine activity (Lalani *et al.* 2000; Tortorella *et al.* 2000). The persistent prevalence of undetectable Japanese encephalitis virus (JEV) inside peripheral macrophages and the significant absence of cell death while in the blood stream is a major cause of concern in detecting JEV infection. Studies have shown that cytokine/chemokine modulation is an important mediator of immune evasion by this virus. Monocyte chemotactic protein 1 (MCP1) and interleukin 6 (IL6) are down-regulated, causing inability to recruit mononuclear leukocytes and other components of the peripheral immune system, and interleukin 10 (IL10), an anti-inflammatory cytokine, is up-regulated, thus inhibiting macrophage activation and antigen presentation (Dutta *et al.* 2010).

Apoptosis, a mechanism of controlled cell death can act as an early innate immune response against cellular perturbations by viral infection. However, viruses have devised ways to inhibit apoptosis. The immune evasion strategies at the apoptotic level include inhibition of caspases, up-regulation of the anti-apoptotic bcl2, blocking of TNF receptors and inactivation of pro-apoptotic IFN-induced PKR and the tumour suppressor p53 (Alcami and Koszinowski 2000; Everett and McFadden 1999).

4. Aspects of epigenetic viral immune evasion: cycle of acetylations and methylations

Emerging evidence indicates that programmed DNA rearrangements, imprinting phenomenon, germ line silencing, developmentally cued stem cell division, and overall chromosomal stability and identity are all influenced

by epigenetic alterations of the underlying chromatin structure (Jenuwein and Allis 2001). Retroviruses and several DNA viruses are capable of integrating their genome into the host genome. The host, unable to differentiate self from non-self, helps the packaging of the viral DNA into nucleosomes or nucleosome-like structures involving histones (Oh and Fraser 2008; Dahl *et al.* 2007; Imai *et al.* 2010). Once inside the host genome, viral gene expression can be regulated just like its host. The virus can stay latent by silencing its gene or can robustly proliferate by activating it. Viral DNA uses not only host transcription factors but also epigenetic regulators. The effects of viral epigenetic control of gene expression also extends to regulating host gene expression, often by silencing host immune response genes present in chromosomal clusters (Wong *et al.* 1999). Transcriptional silencing by methylation of DNA and chromatin remodeling by HDACs leading to inhibition of DNA-binding of some transcription factors has been shown to have a vital role in suppression of the host's innate immune response to infection, especially viral infection. The following are some currently known viruses that exhibit unique epigenetic immune evasion mechanisms to survive and propagate in their host.

4.1 *Viral CpG island methylation paradigm*

Several DNA viruses and retroviruses integrate their genome into the host genome, resulting in the formation of a latent provirus capable of shutting down its transcription at will. Thus, while virus titer may intermittently fall and make their detection difficult, a reactivation of provirus will give rise to increasing viral load and infection. The inactivation of virus genome occurs via methylation of the viral promoter CpG island and recruitment of associated inhibitory complexes (figure 2). The following are some viruses that are able to elude an immune response in the above manner.

4.1.1 *Human immunodeficiency virus (HIV):* In the case of HIV-1, $CD4^+$ T-cells are the reservoirs of latent virus particles (Kauder *et al.* 2009). The existing hypothesis for the latent infection of $CD4^+$ T-cells is that the virus infects T-cells just prior to their natural switch to a quiescent state or naïve T-cells undergoing differentiation during thymopoiesis (Pearson *et al.* 2008; Margolis 2010). The HIV viral activator Tat is a very potent activator of gene expression and interacts with HATs and HDACs to derepress inhibition of transcription, while the HIV promoter is very responsive to cellular activators of transcription such as TNFα and NFκB (Romani *et al.* 2010). Thus, transcriptional regulatory mechanisms are required to allow HIV to establish and maintain a persistent latent infection, and studies have shown the importance of histone-modifying and DNA-methylating enzymes in this respect (Archin and Margolis 2006). Such latent infection renders highly active anti-retroviral therapy (HAART) ineffective. Experiments have revealed that two CpG islands flank the HIV-1 transcription start site, and a methyl CpG domain protein 2 (MBD2) has been identified as a regulator of HIV-1 latency. During latency, a MBD2 and HDAC2 complex has been found at one of these CpG islands. Studies with small molecule inhibitor of methylation, 5-aza-2deoxycytidine (aza-CdR), have confirmed that cytosine methylation and MBD2 are epigenetic regulators of HIV-1 latency. NFκB signalling is responsible for HIV-1 reactivation, but a significant proportion of the latent HIV-1 remains silent even when NFκB is activated. In the latent state, HDAC1 is recruited to the HIV-1 promoter by several sequence specific factors including NFκB p50 and CBF-1 (CSL family protein). MBD2, which is also recruited to the HIV-1 promoter site via a hypermethylated CpG island, silences transcription by recruitment of HDAC2 and the nucleosome remodeling and deacetylase (NuRD) complex. TNFα, an activator of latent HIV-1, on its own, can reactivate only a small percentage of the cell population, ranging from 16% to 41%. Aza-CdR, an inhibitor of methylation, could reactivate latent HIV-1, but on its own showed little effect. In contrast, dual treatment with both TNFα (activator of NFκB) and aza-CdR induced a dramatic increase in HIV-1 gene transcription.

In addition to the above mechanisms involving MBDs and HDACs, trimethylation of the ninth lysine of histone 3 (H3K9) by a histone methyltransferase (HMT) Suv39H1 is also responsible for HIV-1 gene silencing and latency (Lachner *et al.* 2003; Jenuwein 2006; Lee, Teyssier *et al.* 2005). Further experiments have shown the involvement of another HMT, G9a, which has a greater influence on histone methylation than Suv39H1 (Tachibana *et al.* 2001). It was shown that G9a knock-down was associated with loss of Suv39H function (Gazzar *et al.* 2008). This data suggested a

Figure 2. The methylation paradigm in the HIV system: **(a)** Latent virus: The HIV gene integrates into the host genome. Its transcription start site has CpG islands that are methylated by DNMTs, and bound by methyl-binding proteins such as MBD2. A inhibitory complex forms containing HDACs and other co-inhibitors like NuRD. This gives rise to latent provirus. **(b)** Virulent virus: In the presence of stimulation, such as TNFα, the complexes inducing latency such as HDAC and MBD2 are removed from the viral promoter region. Tat interacts with HDACs to remove them from the inhibitory complex. It also interacts with CBP/p300 and activates RNA polymerase complex to initiate transcription from provirus template. **(c)** Combinational therapy for AIDS—a major setback in anti-retroviral therapy: By administering a HDACi such as valproic acid and a DNMTi such as 5-azacytidine, in combination with HAART, an effective treatment for AIDS can be deviced. While the HDACi and DNMTi derepress provirus transcription, HAART detects and inhibits viral replication and propagation in host.

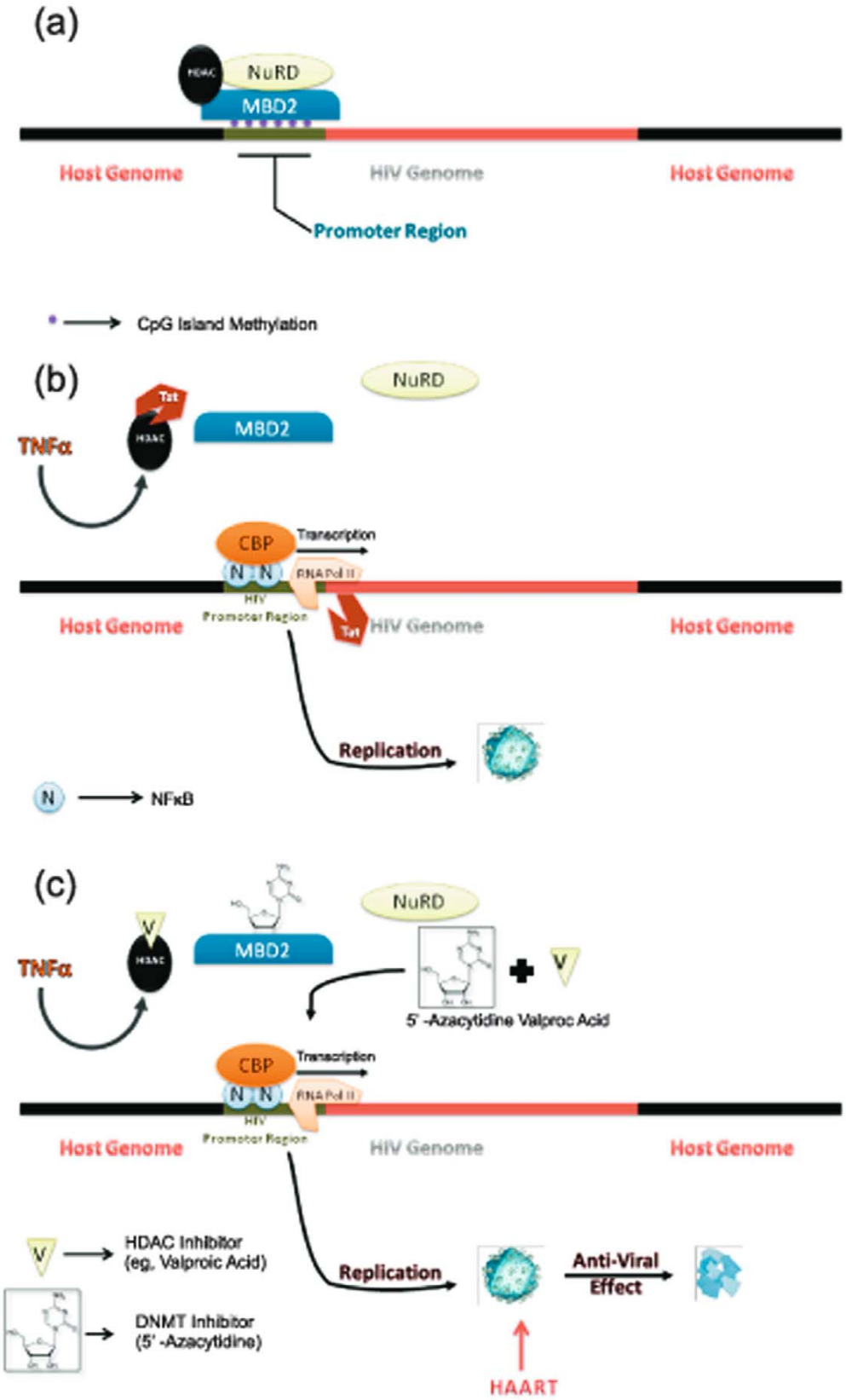

Figure 2. For caption, *see* page No. 650.

downstream location of Suv39H1 in relation to G9a. Thus, the proposed mechanism of HIV-provirus silencing entailed initial recruitment of G9a followed by dimethylation of histone H3 (H3K9me2), which could be recognized by a heterochromatin protein complex containing a heretochromatin protein (HP1) and HDACs (Rea *et al.* 2000; Ogawa *et al.* 2002; Roopra *et al.* 2004; Sampath *et al.* 2007; Gazzar *et al.* 2008), followed by recruitment of Suv39H1, thus converting a silent euchromatin into a heterochromatin. The role of G9a may thus be very significant in the establishment of latency of HIV-1 (Imai *et al.* 2010).

4.1.2 *Bovine leukemia virus (BLV):* BLV is a retrovirus closely related to the human T-cell leukemia virus type 1 (HTLV1), a tumorogenic virus affecting humans. It is responsible for causing infectious mononucleosis and B-cell leukemia in cattle. Similar to the human immunodeficiency virus, the BLV evades immunity through genomic integration and viral latency (Merimi *et al.* 2007). Studies using TSA (an HDAC inhibitor) and 5 azacytidine (a DNA methyltransferases [DNMT] inhibitor) have revealed a mechanism of viral gene expression involving chromatin remodeling. Silencing of viral gene expression has been proposed as a mechanism that leads to immune evasion. BLV provirus, during latency, does not seem to integrate at specific sites of the host genome. BLV retroviral transactivator Tax has been shown to be functionally homologous to the HIV1 Tat protein in having a relaxing impact on epigenetic silencers of integrated provirus. Transcriptional regulation at the HTLV1 promoter sequence is mediated through the binding of Tax with HDACs (Ego *et al.* 2002; Agbottah *et al.* 2006; Lemasson *et al.* 2006; Van Lint 2000). In HTLV1 infection, HDAC1 directly interacts with Tax, increasing levels of acetylated histones H3 and H4 in the vicinity of the HTLV1 LTR (Lu *et al.* 2004).

Activation of Tax in BLV by treatment with HDAC and DNMT inhibitors causes derepression of silenced genes in tumour cells. Whether or not it may help in limiting tumour progression remains to be seen. Progress in clinical treatment is possible especially in combination with chemotherapeutic drugs.

4.1.3 *Epstein–Barr virus (EBV):* EBV infects the host and establishes long-term latency in B-lymphocytes. EBV alternates between latency and the lytic replication, and during latency, the viral genome is largely silenced by the host-driven methylation of CpG islands. Infection of EBV is common throughout the human population, and EBV is the causative agent of infectious mononucleosis and is linked to malignancies such as endemic Burkitt Lymphoma (BL), nasopharyngeal carcinoma (NPC) and Hodgkin disease (HD) (Karlsson *et al.* 2008). In BL cells, the EBV genome is heavily methylated and very few viral genes are expressed, and this is mediated in part by methyl-CpG-binding proteins with methylated DNA, leading to transcriptional silencing and chromatin remodeling. EBV nuclear antigen 3C (EBNA3C) has been shown to repress EBV Cp latency-associated promoter elements, and *in vitro* studies have shown that it forms a complex with HDAC1 to repress the transcription from the Cp promoter (Radkov *et al.* 1999).

4.2 *Host CpG island methylation paradigm*

There are other viruses which modulate immune responses by suppressing expression of certain immune response genes and cytokines. Some cancer-causing viruses may suppress apoptotic proteins (figure 3), while others may inhibit anti-viral proteins. The above are achieved by the interaction of viral proteins with epigenetic modulators of gene expression especially methyltransferases, which are responsible for methylating host promoter CpG islands.

4.2.1 *Hepatitis B virus (HBV):* HBV, of the Hepadnaviridae family causes hepatocellular carcinoma in humans. The hepatitis B virus X protein (HBx) plays an important role in HBV-mediated hepatocarcinogenesis (Block *et al.* 2003; Kim *et al.* 2010). HBx can affect transcription of several genes involved in transformation, cell cycle regulation, apoptosis and cell adhesion through its association with transcriptional activators (Haviv *et al.* 1998). HBx also interacts with and activates several signalling molecules that lead to transcriptional up-regulation of a number of cellular genes, especially those of growth factors and oncogenes (Benn and Schneider 1994). HBx can epigenetically regulate inactivation of tumour suppressor protein retinoblastoma (Rb) via the down-regulation of a cellular senescence protein $p16^{INK4a}$, and by this mechanism overcomes stress-induced premature senescence (SIPS). $p16^{INK4a}$ is a major determinant of senescence for lymphocytes, macrophages and astrocytes, and its repression is a chief cause of HBV-induced immune evasion and cancer (Kim *et al.* 2010).

Methylation anomalies play a fundamental role in tumorigenesis and immune evasion. A strong correlation exists between HBV infection and epigenetic alterations of tumour suppressor genes including $p16^{INK4a}$ (Shim *et al.* 2003). HBx has been shown to activate expression of DNMT1, which methylates $p16^{INK4a}$ (Lee *et al.* 2005). Apparently, DNMT1 is also up-regulated in response to the CpG islands of HBV DNA as a possible innate immune response to infection (Liu *et al.* 2009) and, contradictory to its purpose, acts instead in enhancing HBV-mediated hepatocarcinogenesis.

4.2.2 *Human papillomavirus (HPV):* HPV produces infection in the stratified epithelium of the skin or mucous membrane. HPV is a cause of nearly all cases of cervical

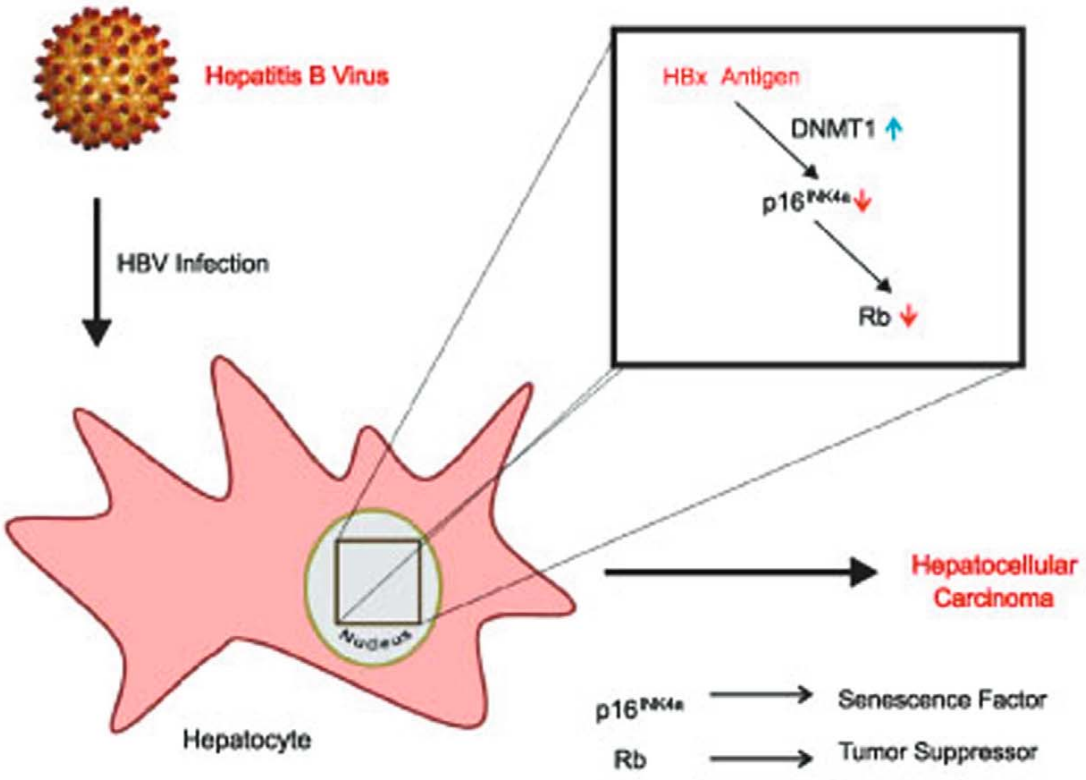

Figure 3. Host CpG island methylation in HBV infection: During HBV infection, the HBx antigenic protein up-regulates DNA methyltransferases (DNMT1) expression. P16INK4a, a senescence factor is down-regulated, which subsequently down-regulates Rb, a tumour supressor.

cancer (Walboomers *et al.* 1999), and is another virus that shows innate immune evasion strategies. Type-1 interferon signal transduction has been shown to be a likely target of viral oncoproteins E6 and E7 of high-risk HPV. HPV18 E6 prevents JAK-STAT1/2 tyrosine phosphorylation (Li *et al.* 1999). Studies on HPV16 E6 encoding cells have suggested that IFN-κ expression is suppressed by *de novo* methylation within a CpG-rich area near the transcriptional start site, IFN-κ being the only keratinocyte-specific IFN involved in innate immunity. Inhibition of this pathway may represent an early and central event in the development of cervical cancer (Rosl *et al.* 1993; Rincon-Orozco *et al.* 2009). E6 has wider functions related to the ubiquitin-proteosome system. It binds to the host protein E6-AP, a member of the HECT (homologous to the E6-AP carboxyl terminus) domain E3 ligase protein family and possibly other ubiquitin ligases. E6-AP ubiquitinates p53 and PDZ family proteins including hDIg, hScribble and hMAGI, designating them to proteosomal degradation (Lin *et al.* 2009; Werness *et al.* 1990). This reduces the level of these key cell cycle regulators without their mutation.

Genetic evidence has suggested that HDAC1 and HDAC2 interact with E7 and that these interactions are critical for E7-mediated transformation (Lin *et al.* 2009). E7 binds to pRb, HDAC1 and HDAC2 (Dyson *et al.* 1989). It diminishes the tumour suppressor retinoblastoma protein (pRb) levels through proteosomal degradation (Huh *et al.* 2007). HDAC1 and HDAC2 may not directly interact with E7. They bind to E7 through the interaction of the Mi2β protein, a component of the mammalian NuRD chromatin remodeling complex (Brehm *et al.* 1999; Lin *et al.* 2009) and bring about gene suppression.

4.3 *Host–viral acetylation–deacetylation paradigm*

Viral proteins are multifunctional, and several viruses express proteins that have been shown to interact with HATs and HDACs, not only to modulate host immunity but also to enhance viral gene expression (figure 4). The following are very interesting examples of viral–host protein–protein interactions bringing about immune evasion and viral pathogenesis.

4.3.1 *Simian virus 40 (SV40):* SV40 is a polyomavirus, with DNA as genetic material, and having the potential to

cause tumours in their hosts (monkeys or humans) (Valls *et al.* 2007). The SV40 large T-antigen (T Ag) is a 708-amino-acid multifunctional oncoviral protein involved in numerous viral and cellular processes, including viral replication, transcriptional activation and repression, and blockade of differentiation and cell transformation (Moran 1993). T Ag can be acetylated by CBP in a p53-dependent manner (Poulin *et al.* 2004). The T Ag along with other viral oncoproteins undergo complex interactions with various intracellular cell control proteins (Ali and Decaprio 2001) and transcriptional regulators such as p53 (Levine 1990; Sheppard *et al.* 1999), pRb and Rb-related proteins p107 and p130 (Decaprio *et al.* 1988; Ludlow *et al.* 1990; Cobrinik *et al.* 1992) and CBP/p300 (Yaciuk *et al.* 1991; Eckner *et al.* 1996; Avantaggiati *et al.* 1996). The CBP/p300 is a coactivator protein involved in both proliferative and differentiation pathways, and contains HAT activity. CBP/p300 is ubiquitously expressed and regulates a broad spectrum of biological activities such as proliferation, differentiation, cell cycle control and apoptosis. SV40 oncoproteins select HAT enzymes as cellular partners, in some cases disrupting enzymatic activity. The E1A antigen can increase, decrease or redirect CBP/p300 HAT activity (Hamamori *et al.* 1999; Ait-Si-Ali *et al.* 1998; Chakravarti *et al.* 1999), while T Ag interacts with CBP to increase its HAT activity (Valls *et al.* 2003). CBP/p300 can acetylate several viral oncoproteins such as E1A (Zhang *et al.* 2000) and T Ag (Poulin *et al.* 2004). However, by interacting with CBP/p300, T Ag affects the transcriptional levels of the cAMP-responsive promoter. T Ag down-regulates CBP/p300-mediated transcriptional activity (Eckner *et al.* 1996; Avantaggiati *et al.* 1996). This repression is accompanied by histone H3 deacetylation and is TSA-sensitive. Along with the T Ag, HDAC1 counteracts CBP transactivation function. HDAC1 is also responsible for the repression of thymidine kinase (TK) and platelet-derived growth factor (PDGF) *β*-receptor promoters by chromatin deacetylation. Thus, it can be seen that the T Ag can interact with both HAT (Avantaggiati *et al.* 1996; Eckner *et al.* 1996; Valls *et al.* 2003) and HDAC activities (Valls *et al.* 2007). This characteristic of the T Ag to show a dual nature may actually be beneficial in stimulating growth and bringing about efficient and rapid changes, by activating one set of genes while repressing another. This enables the virus to not only repress the host innate immunity by global inhibition of immune response genes by HDAC1 but also to activate several viral genes by acetylation of viral proteins by HAT activity of CBP/p300.

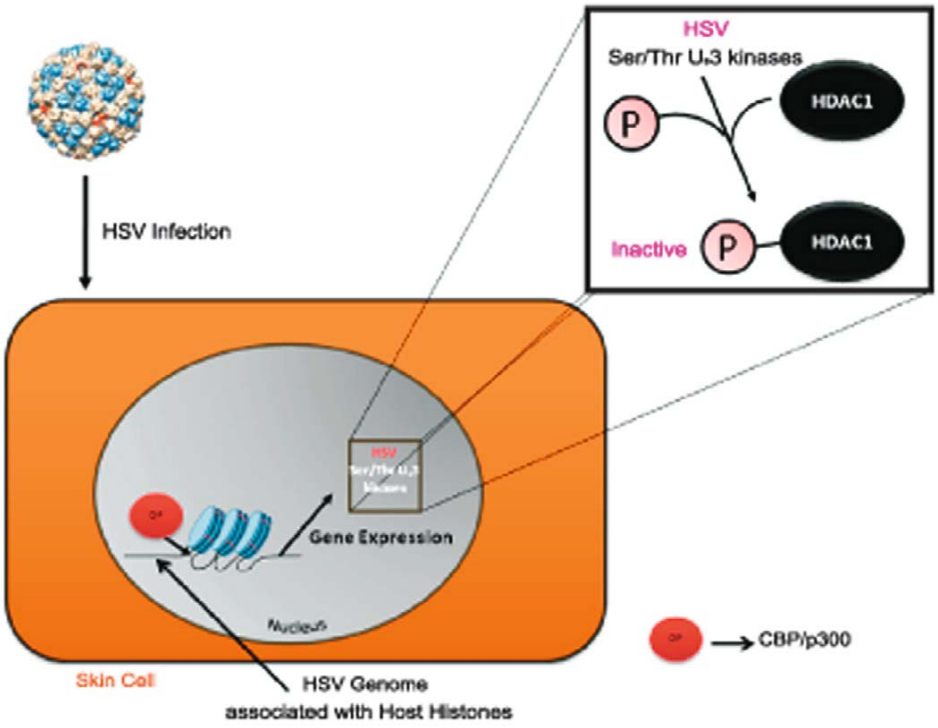

Figure 4. Host–viral acetylation–deacetylation on HSV infection: HSV genome associates with histone proteins, and CBP/p300 histone acetyltransferases activity is essential to promote transcription. Moreover, HSV gene products Ser/Thr Us3 kinases are capable of inhibiting HDAC suppressor activity by phosphorylating them. This not only enhances expression but also ensures more potent pathogenesis.

4.3.2 *Herpes simplex virus (HSV):* HSV is a major cause of sexually transmitted disease in the world today. It belongs to the family Herpesviridae and is a double-stranded DNA virus that undergoes its replication cycle in the nucleus of infected cells. Upon fusion of viral and host membranes the linear genome in the nucleocapsid is injected into the cytoplasm. Along with the genetic material are released preformed tegument proteins that have important functions in interfering with the host defences and stimulating viral gene expression. Studies have shown that the HSV genome on entering the nucleus of its host associates itself with host histone H3 or modified H3 (Herrera and Triezenberg 2004; Huang *et al.* 2006; Kent *et al.* 2004). However, after replication initiates, histones do not appear to be associated with newly replicated viral DNA (Oh and Fraser 2008). During lytic infection, p300 and CBP HATs are recruited to the immediate early gene promoters (Herrera and Triezenberg 2004). Studies to show HAT activity using curcumin as a HAT inhibitor have illustrated the association of chromatin remodeling factors with HSV-1 genome transcription (Kutluay *et al.* 2008). Histone deacetylases also have a role to play in the regulation of HSV-1 gene expression. Various groups have reported that HDACs are involved in repression of viral genome through the deacetylation of lysine residues on histone tails (Gu *et al.* 2005; Gu and Roizman 2007, 2009; Poon *et al.* 2006; Poon *et al.* 2003). However, herpesvirus such as HSV-1 has developed various mechanisms to block the HDAC repressor activity. HSV-1 Ser/Thr U_s3 kinases are capable of indirectly phosphorylating HDAC1 and HDAC2 thus rendering them inactive (Pflum *et al.* 2001; Poon *et al.* 2006). HSV-1 U_s3 kinases have been demonstrated to activate cellular protein kinase A (PKA) (Benetti and Roizman 2004). This allows for vigorous gene expression and rapid pathogenesis by novel HSV-1 immune evasion strategies.

4.3.3 *Varicella zoster virus (VCZ):* VZV, belonging to the family Herpesviridae, infects humans, causes chicken pox in children and shingles in adults. It contains a large double-stranded DNA genome that replicates in the host cell nucleus. Once the viral genome enters the host nucleus, host proteins rapidly act to shut down transcription from viral DNA, and this consequently blocks or impairs replication (Walters *et al.* 2009). The major host proteins that have been shown to have such properties are HDACs, and efficient VZV gene expression, as with other herpesviruses, depends on the inhibition of HDACs (Hobbs and DeLuca 1999; Gwack *et al.* 2001; Poon *et al.* 2003; Danaher *et al.* 2005). Herpesvirus have evolved a range of mechanisms to obstruct the gene-silencing properties of HDACs (Gu *et al.* 2005; Gu and Roizman 2009; Gu and Roizman 2007; Poon *et al.* 2006; Poon *et al.* 2003). By phosphorylating HDACs via HSV-1 Ser/Thr U_s3 kinases, the HSV-1 virus has evolved a successful strategy to evade HDAC repressor activities (Poon *et al.* 2006; Poon *et al.* 2003). VZV encodes ORF66p kinases, orthologs of HSV-1 Ser/Thr U_s3 kinases that are required for the phosphorylation of HDAC1 and HDAC2 (Stevenson *et al.* 1994; Pflum *et al.* 2001; Ogg *et al.* 2004; Schaap *et al.* 2005). Autonomous expression of ORF66p has shown marked hyperphosphorylation of HDAC1 and HDAC2, and its kinase activity has been shown to be responsible for it. ORF66p may not directly transfer phosphate groups to HDAC1 and HDAC2, and possibly acts via activating a cellular kinase or pathway that, in turn, hyperphosphorylates HDAC1 and HDAC2 (Walters *et al.* 2009).

4.4 *Epigenetic immune control by ssRNA virus*

RNA viruses are relatively small and less complicated than DNA viruses, and yet they have elaborate epigenetic immune evasion strategies, as shown in various studies. They are able to regulate host immune gene expression by altering methylation and acetylation states of genes (figure 5). Much needs to be studied to produce some clarity in their mechanism. Below are some excerpts from different studies going on today regarding this aspect of viral immune evasion.

4.4.1 *Hepatitis C virus (HCV):* HCV is the causative agent for hepatitis C in humans. Chronic infection is associated with liver fibrosis and cirrhosis. Hepatitis C and hepatitis B viruses share similar names because they cause live inflammation in general, but they are distinctly different viruses genetically and clinically. The hepatitis C virus is a small (+)ssRNA virus of the Flaviviridae family which can cause epigenetic modifications in its host. The role of host miRNA in facilitating HCV replication is already well-documented and elaborated later in Section 6 (Jopling *et al.* 2008). Studies on host histone acetylation and DNA methylation status on HCV infection is not well studied yet. Of the few studies performed, the work of Shuo Li *et al.* seems to stand out in the identification of a regulatory T-cell (Treg)-specific demethylated region (TSDR), an evolutionarily conserved element within the *FOXP3* gene locus that is methylated in most T-cells in various degrees, except in hepatitis-C-virus-activated Treg cells (Li *et al.* 2009). The transcription factor FOXP3 plays an important role in the development and function of these cells, and it is used as a specific marker for their identification. *FOXP3* TSDR demethylation and the consequent expression of FOXP3 are very exclusive to activated Treg cells (Baron *et al.* 2007). Treg cells, a specialized subpopulation of T-cells, act to suppress activation of immune system in an effort to maintain immune system homeostasis and tolerance to self-antigens. Their activation by HCV can only mean a highly

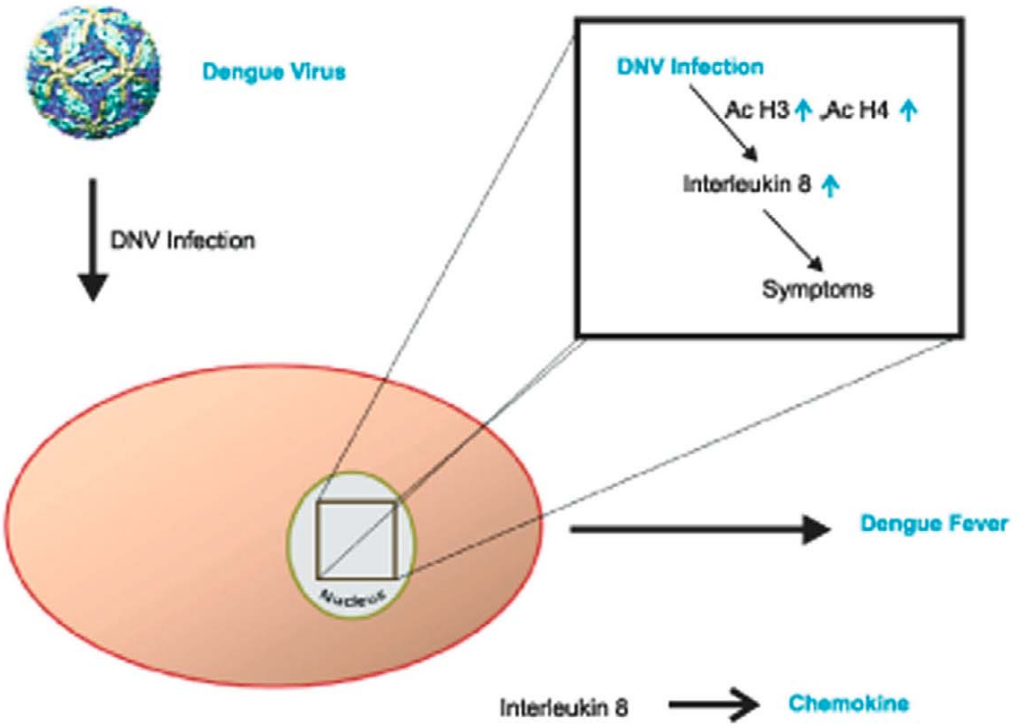

Figure 5. ssRNA virus paradigm of dengue virus: The dengue virus model of epigenetic immune evasion involves an up-regulation of acetylated histones H3 and H4. This has been correlated with an increasing expression of interleukin 8 secretion. High levels of IL8 are probably responsible for plasma leakage that happens as a result of DHF and dengue shock syndrome..

adapted mechanism of viral immune evasion down the epigenetic route.

4.4.2 *Dengue virus (DNV):* Another member of the family Flaviviridae, DNV is the causative agent of dengue fever (DF) and dengue hemorrhagic fever (DHF), which are febrile diseases largely prevalent in the tropics. It has been shown that dengue-virus-2-infected endothelial cells produce interleukin-8 (IL-8) (Huang *et al.* 2000). IL-8 is a chemokine and a major mediator of the inflammatory response. IL-8 has chemoattractant activity for neutrophils, and patients with DF and DHF demonstrated degranulation of neutrophils (Juffrie *et al.* 2000). Transcription of IL-8 gene can be regulated by the degree of binding of acetylated histones (Fusunyan *et al.* 1999). It is not known whether DNV infection in monocytes inhibits HDAC activity. Levels of histone acetylation of the IL-8 promoter are very low in mock-infected cells, and the status of H3 and H4 acetylation seem to reflect the expression of IL-8 (Timmermann *et al.* 2001). Increased IL-8 gene expression is associated with increased H3 and H4 acetylation in DNV-infected cells, and this can be shown by an increased IL-8 mRNA levels and secretion of the chemokine. This is a unique mechanism of transcriptional control not previously shown in cytosolic RNA viruses (Bosch *et al.* 2002). Whether this strategy of host transcriptional control seen after DNV infection is associated with an immune evasion strategy is yet to be reported, but it probably plays a role in the pathogenesis of plasma leakage seen in dengue hemorrhagic fever and dengue shock syndrome (Bosch *et al.* 2002).

5. Viruses and the miRNA paradigm

MiRNA are short ribonucleic acid (RNA) molecules about 22 nucleotides long. The human genome encodes more than 700 miRNAs. RNA stem loops transcribed from introns of protein and non-protein-coding genes or even exons are cleaved to form miRNAs (Rodriguez *et al.* 2004).

Viruses can also encode miRNAs. Viral miRNAs serve two major functions. They can inhibit the expression of cellular factors that play a role in cellular, innate or adaptive anti-viral immune responses. Natural killer (NK) cell ligand MHC class I chain-related protein B (MICB) is down-regulated by miRNAs encoded by EBV, Kaposi's sarcoma-associated herpes virus (KSHV) and human cytomegalovirus (HCMV) (Nachmani *et al.* 2009), while EBV encodes miRNA that can inhibit pro-apoptotic protein

PUMA (Choy *et al.* 2008). Such down-regulation of the host gene expression is potentially very helpful to virus propagation. Secondly, viral miRNAs can inhibit expression of viral proteins, including key viral immediate-early or early regulatory proteins. HSV1 down-regulates immediate-early transactivators ICP0 and ICP4 in latently infected cells by viral miRNAs that are expressed at high levels during latency, but not during productive viral replication, stabilizing the latent state as a result (Umbach *et al.* 2008). Several polyomaviruses down-regulate the expression of the viral T antigens and key early transcription factors at late stages in the viral replication cycle. In the case of SV40, SVmiRNAs accumulate at late times of infection. They are perfectly complementary to viral mRNAs and target those for cleavage. The expression of viral T antigen is reduced without having any effect on the yield of infectious virus particles. Studies have shown that wild-type SV40-infected cells are less susceptible to lysis by cytotoxic T-cells than mutants lacking SVmiRNAs. Wild-type virus particles also elicit less cytokine production by such cells (Sullivan *et al.* 2005). There is, of course, not enough evidence to support the role of miRNA in replication and pathogenesis of viruses.

Table 1 Summary of the epigenetic viral immune evasion strategies

Virus	Viral strategy*	Host epigenetic agents targeted*	Immune evasion
1. Viral CpG island methylation paradigm			
HIV Family: Retroviridae	Induction of latency by viral genome integration.	Histone H3, HDAC1, HDAC2, MBD2, HMTs, NFκB, Suv39H1, G9a.	Transient absence of viral gene products due to DNA methylation, histone deacetylation and histone methylation.
BLV Family: Retroviridae	Viral latency, viral Tax protein acts as activator.	Histones, HDACs.	Transient absence of viral gene products due to DNA methylation and histone deacetylation.
EBV Family: Herpes-viridae	Viral latency and gene silencing by viral protein EBNA3C.	Methylation of CpG islands, methyl binding proteins, HDAC1.	Transient absence of viral gene products due to DNA methylation and histone deacetylation.
2. Host CpG island methylation paradigm			
HBV Family: Hepadna-viridae	Host genome methylation via HBx protein	DNMT1, $p16^{INK4a}$, E-cadherin, Rb.	Inhibition of senescence and apoptotic proteins.
HPV Family: Papilloma-viridae	E6 and E7 oncoproteins suppress IFN-κ by methylation of CpG island.	CpG island of IFN-κ promoter, HDAC1, HDAC2, JAK-STAT1/2.	Inhibition of Type1 IFN signal transduction.
3. Host viral acetylation-deacetylation paradigm			
SV40 Family: Polyoma-Viridae	Actions of large T antigen and E1A to inhibit immune response genes, while activating viral transcription and replication.	CBP/p300, HDAC1, TK, PDGF β-receptor.	Dual action inhibiting innate immunity, while enhancing viral gene expression.
HSV Family: Herpes-viridae	Suppression of HDAC repressor activity on viral genome by Ser/Thr U_s3 kinases.	Histone H3, CBP/p300, HDAC1, HDAC2.	Obstruction of HDAC inhibition of viral genome.
VZV Family: Herpes-viridae	Suppression of HDAC repressor activity on viral genome by ORF66p kinases.	HDAC1, HDAC2.	Obstruction of HDAC inhibition of viral genome.
4. Epigenetic immune control by ssRNA virus			
HCV Family: Flaviviridae	Host gene demethylation	Treg cell FOXP3+ TSDR.	Activation of Treg cells, modulators of immune system.
DNV Family: Flaviviridae	Induction of increased acetylation of histones.	Histones H3 and H4, Il-8.	Increased IL-8 production playing important role in pathogenesis (possible immune evasion strategy linked)

* The list may not be exhaustive – factors having sound evidence in favour of them have only been included.

In fact, the mutant polyomavirus lacking its only miRNA replicated indistinguishably from wild-type in infected cells (Sullivan *et al.* 2009).

Alternatively, viruses have a more established role in hacking into the miRNA pool of the host to promote its replication. Liver-specific miRNA122 has an extensive role in the regulation of lipid metabolism, hepatocarcinogensis and hepatitis C virus replication. MiRNA122 binds to the 5 end of the hepatitis C virus genome, resulting in increased gene expression. In fact, there are two miRNA122 binding sites on the HCV genome and they carry out cooperative postion-dependant functions (Jopling *et al.* 2008). Liver miRNA122 has effects on hepatitis B virus replication but of a different manner than that of HCV. Overexpression studies of miRNA122 have shown inhibition of HBV viral replication and reduction in HBV viral load, while depletion has resulted in higher HBV replication (Qiu *et al.* 2010). Such modulation of HBV replication by miRNA can be a means of viral immune evasion to escape antigen presentation, or can be an effective strategy in limiting HBV replication.

It is still unclear, though, as to how viruses deal with potentially inhibitory effects of the large number of cellular miRNAs, prospective targets pf viral RNA genomes or mRNAs.

6. Epigenetic therapeutics: use of HDAC inhibitors as or in combination with anti-viral drugs

Chemical compounds that interfere with the epigenetic immune evasion strategies of pathogens can be used as drugs against infections caused by them. One such class of compounds are the HDAC inhibitors (HDACi). "Classical" HDACi acting on Zn^{2+}-dependent HDACs (HDACs 1-11) include short-chain fatty acids, such as sodium butyrate and valproic acid (VPA); hydroxamic acids, such as trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA); benzamides, such as MS275; and cyclic tetrapeptides such as trapoxin and depsipeptide (Bolden *et al.* 2006; Minucci and Pelicci 2006; Walkinshaw and Yang 2008; Mai and Altucci 2009). Inhibitors of Zn^{2+}-dependent HDACs act by chelating or displacing the Zn^{2+} present in the catalytic site. Specificity of such HDACi arise from interactions with the cap region that is adjacent to the catalytic site (Richon and O'Brien 2002; Bottomley *et al.* 2008; Schuetz *et al.* 2008).

One of the major areas of research on HDACi as anti-virals has been in the case of HIV. HIV infection today can be dramatically ameliorated by HAART. HAART acts by shutting down virus production. The success of HAART has hit a roadblock because of the low level of viral replication in infected cells and the prevalence of latency of HIV in resting CD4+ cells (Routy 2005). Most CD4+ cells are activated after HIV infection and undergo apoptosis. However, a small population of the activated cells return from an activate state to a resting one (Younes *et al.* 2003). HIV genomes integrated into such cells remain indefinitely present as a reservoir capable of HIV replication (Siliciano *et al.* 2003). Valproic acid, an HDACi, has been shown to effectively induce HIV out of latency from resting cells by inhibiting the gene-silencing activity of HDAC2 and its CpG-island-binding complex containing MBD2. As a result, the acetylated histones free the promoter of the latent HIV genome while the demethylated CpG islands allow transcription factors to start gene transcription. This enables detection of HIV particles and their subsequent shutting down and clearing of by HAART. SAHA, another HDACi acting in a similar manner as valproic acid, is also capable of inducing latent viral infection out of HIV and is being considered as an effective and less-toxic alternative for the treatment of HIV patients (Edelstein *et al.* 2009).

7. Discussion and future perspectives

The co-evolution of viruses and hosts has resulted in many anti-viral mechanisms that shut down the replication machinery of the virus. For the same reason, different viruses have evolved devices to counter host innate immune responses. Most of the strategies employed are very complex, and they still elude the greatest efforts of the scientific community at unraveling them. The viral genome can be considered to be mutated half-brothers of the host genome, and this enables them to efficiently utilize the host replication and transcriptional machinery for their propagation. The mechanisms of epigenetic control of gene expression continue to baffle scholars. Yet, pathogens have intrinsically incorporated these machineries to propagate their species. Recent efforts have discovered the various interactions that pathogens have with the host on an epigenetic level, and it has been observed that such studies may provide novel and more effective attempts at drug discovery against such pathogens.

Small pox, caused by members of the family Poxviridae, has been eradicated through vaccination. Poliomyelitis, caused by Poliovirus, can be controlled by vaccination. However, it does not have any cure. A vast majority of viruses are constantly undergoing mutation and are evolving into newer and more-virulent strains. Development of vaccines against such pathogens is a complicated task, and anti-viral drugs a near impossibility. In these circumstances, scientists have discovered a common evolutionarily conserved mechanism of viral host immune evasion, and that is through the modulation of expression of host anti-viral effector proteins through epigenetic silencing. Thus, the challenge today is in the discovery of unique inhibitors of epigenetic silencers such as HDACs and MBDs that can

assist activation of host immune reponse genes by interfering with the pathogenesis of viruses.

As explained above, viruses of the families Retroviridae (HIV and BLV), Polyomaviridae (SV40), Hepadnaviridae (HBV), Herpesviridae (EBV, HSV and VZV) and Papillomaviridae (HPV) show immune evasion tactics by epigenetic means. HCV and DNV of the Flaviviridae family also show epigenetic modulatory capabilities. The influenza A virus (IAV), a (–)ssRNA virus of the Orthomyxoviridae family, has been reported to cause apoptosis in host. During IAV infection, HDAC6, a multi-substrate cytoplasmic enzyme, has been shown to undergo cleavage by caspase 3 (Husain and Harrod 2009). HDAC6 belongs to class IIb HDACs, and its suppression has been reported to be beneficial for viral infection (Valenzuela-Fernández *et al.* 2008). Many other viruses have the ability to disrupt the host's innate immunity, although the epigenetic link still remains to be studied in most cases. (+)ssRNA viruses of the Flaviviridae family including the Japanese encephalitis virus (JEV) have the ability to suppress innate immune responses in a way that suggests putative epigenetic mechanisms. Studies involving administration of DNA vaccines (pE, a plasmid encoding the E-protein of JEV which enables anti-E Ab production) have shown strong suppression of humoral and cellular immune responses. T-helper cell response, which mediate major peripheral immune responses, have been shown to be effected (Chen *et al.* 2001). It is yet to be studied whether epigenetic mechanisms are involved in such inhibition of immunity.

There is still much ambiguity over the epigenetic mechanisms of viral immune evasion. It is a great challenge for future scientists to unravel the nuances of viral epigenetics. Most of the discovered mechanisms are still incomplete. The various types of histone modifications other than acetylations and methylations are yet to be well-studied. The roles of the various histone-modifying proteins and DNA methylation proteins are inconclusive to a large extent. HDACs themselves are a large class of proteins that have a wide range of unidentified protein-modifying functions operating outside the nucleus. Immune genes are present in clusters in chromosomes. A study of the regulation of the immune gene clusters may lead to the development a much larger and complicated mechanism of epigenetic regulation. Studies on HIV and DNA viruses have been pioneering works in the field of viral epigenetics. They has opened up a plethora of questions regarding viral immune evasion and a new chapter in the mechanism of host innate immunity.

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