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REVIEW

Epigenetic mechanisms in virus-induced tumorigenesis

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Abstract About 15–20% of human cancers worldwide have viral etiology. Emerging data clearly indicate that several human DNA and RNA viruses, such as human papillomavirus, Epstein–Barr virus, Kaposi's sarcoma-associated herpesvirus, hepatitis B virus, hepatitis C virus, and human T-cell lymphotropic virus, contribute to cancer development. Human tumor-associated viruses have evolved multiple molecular mechanisms to disrupt specific cellular pathways to facilitate aberrant replication. Although oncogenic viruses belong to different families, their strategies in human cancer development show many similarities and involve viral-encoded oncoproteins targeting the key cellular proteins that regulate cell growth. Recent studies show that virus and host interactions also occur at the epigenetic level. In this review, we summarize the published information related to the interactions between viral proteins and epigenetic machinery which lead to alterations in the epigenetic landscape of the cell contributing to carcinogenesis.

Keywords Epigenetics · DNA methylation · Histone modification · Oncogenetic virus · Human cancer

Viruses and cancer

Cancer research over the past five decades has revealed important role of viral infections in human cancer. Viral etiology of human neoplasms was first discovered at the turn of the nineteenth century, when Ciuffo and co-workers demonstrated that human warts can be transmitted by cell-free filtrates derived from lesions (Ciuffo 1907). Several years later, in 1911, P. Rous identified the first animal tumorigenic virus (Rous sarcoma virus) that induces development of spindle cell sarcoma in birds. The first human tumor-associated virus was discovered more recently, in 1964, by Michael Anthony Epstein and Yvonne Barr and was named Epstein–Barr virus (EBV).

Recent studies have shown the infectious etiology of several cancers. It has been estimated that 15–20% of all human cancers worldwide are caused by oncogenic viruses (Butel 2000). Viruses associated with cancer belong to different phylogenetic groups. They include both DNA viruses, e.g., human papillomaviruses (HPV), hepatitis B virus (HBV), the herpesviruses such as EBV and Kaposi's sarcoma-associated herpesvirus (KSHV), and RNA viruses such as retroviruses, e.g., human T-cell lymphotropic virus 1 (HTLV-1), and the RNA flavivirus, hepatitis C virus (HCV). The causal contribution of the above-mentioned viruses to the development of human neoplasms is now well documented. Besides these, there are other viruses with a potential influence on human carcinogenesis. Recently, an integrated form of a new polyomavirus, MCPyV, has been detected in patients with the Merkel cell carcinoma (zur Hausen 2008; Feng et al. 2008). Other polyomaviruses, such as SV40, JCV, and BKV, and adenoviruses may play possible role in human carcinogenesis as well. Polyomaviruses are tumorigenic under experimental conditions, and their genomic sequences were detected in samples derived from several human cancers, e.g., human osteosarcoma, mesotelioma, brain tumors, prostate cancer, and NHL; however, no definite proof exists that these viruses directly contribute to human cancer (McCabe et al. 2006; Goel et al. 2006; Feng et al. 2008; Jiang et al. 2009). Certain serotypes of adenoviruses are also highly transforming in cell culture and in animal models but adenovirus DNA was generally not detected in human tumor cells. However, one study reported detection

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of adenovirus DNA in pediatric brain tumors (Kosulin et al. 2007), therefore the possible contribution of adenoviruses to human oncogenesis should be considered.

Some viruses, e.g., HBV, HCV, HTLV-1, are linked to a single cancer type whereas some viruses, such as HPV, EBV, and KSHV, contribute to multiple cancer types. Prevalence of several viruses is particularly high in certain cancer types. For example, HPV is associated with 95% of cervical cancers, human HBV and human HCV are associated with 80% of hepatocellular carcinomas (HCCs), and EBV is positive in 30% of Hodgkin's lymphomas (zur Hausen 2006). A summary of the human viruses associated with cancer development is listed in Table 1.

Unlike acute-transforming animal retroviruses, human oncoviruses lead to cancer development with prolonged persistent infections. Additional factors such as environmental carcinogens, host cell mutations, and immune response also take part in viral-associated carcinogenesis. Viral strategies in human cancer development are diverse, depending on virus species and cell type they affect. Despite this, they share many common features. All human tumor-associated viruses encode oncoproteins essential for viral replication that disrupt cellular processes, such as apoptosis and cell-cycle checkpoint control (Butel 2000; McLaughlin-Drubin and Munger 2008). The main cellular targets of viral oncoproteins are p53 and RB, although recent studies also report other targets like nuclear factor κB (NFκB), hTERT, and TRAFs (Oliveira 2007; O'Shea 2005). The oncoproteins play very important role in viral life cycle. Because DNA oncoviruses rely on the cellular DNA replication machinery for propagation and most of them infect quiescent cells, which are not optimal for viral DNA replication, they evolved oncoproteins targeting the central cellular hubs regulating cell growth. This mechanism enables oncoviruses to force quiescent cells into unscheduled S-phase entry thus leading to concomitant DNA viral genome replication with host DNA. Deregulation of apoptosis and cell-cycle checkpoint control induced by tumorigenic viruses subsequently leads to an increase in cellular DNA mutations and genome instability (Butel 2000; Oliveira 2007; O'Shea 2005).

Recent cancer research provides the emerging information on the molecular events underlying the tumorigenic potential of human oncoviruses. During last two decades, significant progress has been made towards understanding the viral oncogenetic mechanisms. It has been demonstrated that the virus/host interactions that contribute to cancer development also occur at the epigenetic level.

The epigenetic state of cancer cell differs significantly from that of the normal cell. Cancer cells are characterized by multiple epigenetic alterations including DNA methylation and histone modification. Compared to the normal cells, cancer cells contain hypermethylated CpG islands in promoters of specific sets of genes and genome-wide hypomethylated DNA mainly in the body of genes and intergenic regions (Suzuki and Bird 2008; Esteller 2007; Kulis and Esteller 2010). The analysis of cancer cells epigenomes also revealed numerous aberrations in histone modifications including histone acetylation and methylation. These epigenetic aberrations lead to inappropriate gene expression that contributes to cancer development (Esteller 2007; Chi et al. 2010; Biancotto et al. 2010).

Increasing evidence reveals that oncogenic viruses also contribute to the epigenetic changes that are characteristic

Table 1 Viruses associated with human cancer development

Virus	Taxonomy	Genome	Human cancer
HPV	*Papillomaviridae*	dsDNA	Cervical cancer, Anal cancer, Penis cancer, Head and neck carcinoma
EBV	*Herpesviridae*	dsDNA	Burkitt's lymphoma, Hodgkin's lymphoma, Posttransplantation lymphoma, Nasopharyngeal carcinoma
KSHV (HHV-8)	*Herpesviridae*	dsDNA	Kaposi's sarcoma, Pleural effusion lymphoma, Multicentric Castleman's disease
HBV	*Hepadnaviridae*	dsDNA	Hepatocellular carcinoma
HCV	*Flaviviridae*	ssRNA	Hepatocellular carcinoma
HTLV-1	*Retroviridae*	ssRNA-dsDNA	Adult T-cell leukemia
MCV	*Polyomaviridae*	dsDNA	Merkel cell carcinoma
SV40	*Polyomaviridae*	dsDNA	Mesothelioma and colon tumors
JCV	*Polyomaviridae*	dsDNA	Brain and colon tumors
BKV	*Polyomaviridae*	dsDNA	Prostate and brain tumors
Adenovirus	*Adenoviridae*	dsDNA	Several serotypes can transform human and rodent cells and cause malignant tumors upon injection into rodents

HHV-8 human herpesvirus 8

for cancer cells. Tumor-associated viruses interfere with host epigenetic machinery and cause aberrations of DNA methylation as well as changes in histone modifications. Many studies have shown that viral oncoproteins induce expression and interact with cellular DNA methyltransferases (DNMTs) as well as histone-modifying enzymes, e.g., histone deacetylases (HDACs), histone acetyltransferases (HATs), histone methyltransferases, and demethylases changing their activity (Burgers et al. 2007; Ferrari et al. 2009; McLaughlin-Drubin et al. 2011). Viral proteins are also able to alter the activity of proteins associated with the chromatin-remodeling complexes and miRNA processing (Flanagan 2007; Javier and Butel 2008; Whitby 2009).

Viruses that are able to integrate their genomes into host DNA often activate host defense mechanism that is responsible for the inactivation of integrated foreign genetic material by DNA methylation (Doerfler 1991a; 1996; 2009). Moreover, viral DNA methylation can be a masking mechanism that helps to avoid viral proteins recognition by the immune system during latent infections (Fernandez et al. 2009).

This review summarizes the information available about the epigenetic mechanisms used by human oncogenic viruses in human tumorigenesis. We describe the interactions between viral proteins and host epigenetic machinery and their consequences for the host cell epigenome and the viral life cycle.

Human papillomaviruses

HPV are small non-enveloped DNA viruses which infect epithelial cells and their life cycle depends on epithelial differentiation and viral–host protein interaction (Doorbar 2005, 2006). More than 100 different types of HPV have been identified and classified into low- or high-risk groups depending on their likelihood of inducing cervical cancer (zur Hausen 2009). Cervical cancer is one of the most common cancer among women worldwide and is strongly linked to infection by high-risk human papillomaviruses, mainly HPV16 and HPV18 types (de Villiers et al. 2004; zur Hausen 2009).

HPV E6 and E7 early proteins are the major HPV oncogenic proteins, which induce proliferation, immortalization, and malignant transformation of the infected cells. The key event in cervical carcinogenesis is integration of HPV genome into the host cell chromosome. In this case, virus is not able to complete its productive life cycle, and viruses are not released from infected cells, but can persist in the host cells and initiate oncogenesis. The integration frequently disrupts the E1-E2 genome region, resulting in a loss of E2 viral gene expression. E2 protein is a transcriptional repressor of E6 and E7 gene expression. Therefore, deregulation of E2 expression leads to an increase in expression of both E6 and E7 oncoproteins. Interactions between high-risk HPV16 E6 and E7 proteins and human tumor suppressor gene products p53 and retinoblastoma (RB), respectively, lead to functional inactivation of these critical cell regulatory proteins and thus contribute to tumorigenesis process.

Epigenetic alterations such as changes in DNA methylation pattern of viral and host genome as well as histone modification are very often associated with HPV infection and cervical carcinogenesis. Methylation of HPV DNA takes place regularly in vivo in cervical cells, clinical samples as well as in cell cultures. (Badal et al. 2003, 2004; Kim et al. 2003; van Tine et al. 2004; Kalantari et al. 2004; Wiley et al. 2005; Turan et al. 2006; Bhattacharjee and Sengupta 2006). It has been suggested that de novo methylation of HPV DNA might be a host defense mechanism for silencing viral replication and transcription or strategy that virus uses to maintain a long-term infection (Remus et al. 1999; Badal et al. 2003). HPV genome does not encode any known protein involved in DNA methylation machinery, therefore it is believed that the viral genome as well as the host genome is methylated by human host cell DNMT (Fernandez and Esteller 2010). The pattern of HPV genome methylation changes and depends on the stage of viral life cycle, and the presence of disease and probably the viral type (Woodman et al. 2007). Viral DNA hypermethylation is more closely associated with carcinomas than with asymptomatic infections or dysplasia (Fernandez et al. 2009). DNA hypermethylation has been observed in long control region (LCR) and L1 region of HPV genome (Badal et al. 2003, 2004; Kim et al. 2003; Kalantari et al. 2004; Bhattacharjee and Sengupta 2006; Turan et al. 2007; Hublarova et al. 2009). In the case of HPV16, LCR has been observed to be methylated in some primary cervical carcinomas, especially at E2-binding sites (E2BS; Bhattacharjee and Sengupta 2006; Brandsma et al. 2009; Fernandez et al. 2009). It has been proved in vitro that DNA methylation of the E2BS sequence inhibits the binding of E2 protein (Thain et al. 1996) and that this methylation is related to the reactivation of E6 and E7 in advanced stages of carcinogenesis induced by HPV16. It has been demonstrated that the use of DNA demethylating agents can induce recruitment of E2 protein to its upstream regulatory region-binding sites and reduce E6 and E7 expression (Fernandez et al. 2009). In the case of HPV18, LCR has been found to be methylated in several primary cell carcinomas and also in immortal descendant cells from primary human foreskin keratinocytes transfected with the entire HPV18 genome. However, the methylation of LCR has not been found in C41 and HeLa cell lines and the level of E6 and E7 was not modified by the treatment with DNA demethylating agents (Fernandez et al. 2009).

Different methylation pattern of L1 sequence has been found in carcinomas, premalignant lesions, and asymptomatic carriers in the case of HPV16 and HPV18 infection. HPV16 L1 sequence is methylated at intermediate level in asymptomatic infection, hypomethylated in precursor lesions, and hypermethylated in carcinomas (Badal et al. 2003; Kalantari et al. 2004). L1 gene of HPV-18 is also hypermethylated in the carcinomas contrasting with its hypomethylated state in asymptomatic infections and unmethylated in precursor lesions. These results suggest that L1 DNA methylation may be a powerful biomarker of the clinical progression of HPV-18-associated disease and possibly HPV-16-associated lesions as well (Turan et al. 2007).

Changes in DNA methylation pattern might also be found in the host genome. Several tumor suppressor genes possessing CpG islands in the promoter region are frequently inactivated by hypermethylation in cervical cancer cells (Szalmás and Kónya 2009; Woodman et al. 2007). Epigenetic silencing of genes involved in cell-cycle regulation (e.g., p16; Nakashima et al. 1999a, b; Nuovo et al. 1999), apoptosis (e.g., DcR1/DCR2, hTERT, p73; Shivapurkar et al. 2004; Widschwendter et al. 2004; Liu et al. 2004), DNA repair (MGMT; Narayan et al. 2003; Virmani et al. 2001), development and differentiation (RARβ; Narayan et al. 2003; Ivanova et al. 2002), hormonal response (ERα; Zambrano et al. 2005) and cellular signaling (RASSF1A; Cohen et al. 2003; Yu et al. 2003), invasion, and metastasis (DAPK; Narayan et al. 2003; Virmani et al. 2001) has been detected in cervical cancer cells. However, it is still not clear if methylation of tumor suppressor genes in cervical cancer cells is induced by HPV viruses or it is an effect of carcinogenesis. Difficulties with distinction may result from the fact that almost all of cervical cancer cells are HPV positive at diagnosis. Therefore, any comparison here will be non-informative opposite to (EBV)-positive and negative gastric cancers; hepatitis C positive and negative hepatocellular carcinomas, and simian virus 40 (SV 40) positive and negative mesotheliomas (Woodman et al. 2007).

Although, there is no evidence for HPV-induced methylation of tumor suppressor genes, it has been proved that HPV viral proteins interact with cellular proteins which are components of epigenetic machinery. For example, HPV16 E7 binds DNA methyltransferase 1 (DNMT1) and stimulates its enzymatic activity (Burgers et al. 2006) and may activate transcription of DNMT1 as well (Robertson 2001; McCabe et al. 2005; Woodman et al. 2007). Moreover, E6 and E7 proteins interplay with histone modification machinery (Table 2). E6 binds to and inhibits HAT proteins

Table 2 Example of interactions between oncogenic viral proteins and host epigenetic machinery

Virus	Viral protein	Epigenetic interaction
HPV	E7	Binds DNMT1 and stimulates DNA methyltransferase activity
		Binds HDACs and Mi2 subunit of Nurd ATP-dependent remodeling complex
		Induces KMD6A and KDM6B histone demethylase expression
		Induces expression of histone methyltransferase EZH2
	E6	Interacts with p300/CBP and inhibits HAT activity
EBV	LMP1	Activates DNMTs 1, 3a, and 3b
	EBNA2	Interacts with p300 and activates transcription
	EBNA3c	Binds HDACs
KSHV	LANA	Activates DNMT3a
		Interacts with SUV39H1, MeCP2, and mSin3
	vIRFs	Binds p300/CBP and inhibits HAT activity
HBV	HBx	Activates DNMT1
		Regulates the expression of DNMT3a and DNMT3b
		Interacts with p300/CBP
		Interacts with HDAC
Adenovirus	E1A	Binds DNMT1 and stimulates DNA methyltransferase activity
		Binds p300/CBP, TRRAP/GCN5, and PCAF HAT complexes
		Binds to p400 and promotes the formation of a Myc–p400 complex at Myc-target gene promoters
	E4ORF3	Stimulates de novo H3K9me3 heterochromatin formation specifically at p53 target promoters
HTLV-1	Tax	Interacts with p300/CBP to repress transcription
		Binds BRG1 subunit of chromatin-remodeling complexes

vIRF viral homologue of interferon regulatory factor

CBP, p300 (Patel et al. 1999; Zimmermann et al. 1999). Furthermore, E7 oncoprotein has been demonstrated to interact with pCAF acetyltransferase and to reduce its acetyltransferase activity in vitro (Avvakumov et al. 2003). E7 can also associate with HDACs. The association between E7 and HDACs results in an increased level of E2F2-mediated transcription in differentiating cells, which is proposed to influence S-phase progression (Longworth et al. 2005). It has been demonstrated that displacing of HDAC from RB by HPV16 E7 protein leads to an increase in H3 acetylation specifically at the E2F-targeted promoters in human foreskin keratinocytes (Zhang et al. 2004). Most recent study demonstrated that human papillomavirus E7 oncoprotein induces KMD6A and KDM6B histone demethylase expression, thus leading to a decrease in H3K27me3 level in HPV16-positive cervical lesions (McLaughlin-Drubin et al. 2011). It has been shown that KMD6B upregulation mediated by E7 oncoprotein correlates with increased expression of the cervical carcinoma biomarker p16INK4A. Also, several HOX genes regulated by KDM6A or KDM6B have been shown to be expressed at higher levels in such cells. Therefore, the authors suggest that HPV16 E7 expression causes epigenetic reprogramming of host cells at the level of histone methylation. HPV16 E7 protein has also been shown to induce expression of histone methyltransferase EZH2 expression in cervical cancer cells; however, the changes in the histone modification pattern have not been examined (Holland et al. 2008). EZH2 overexpression does not result in increased PRC2 activity but enhances PRC4 formation, which has been demonstrated to cause histone H1K26 deacetylation and methylation (Kuzmichev et al. 2005). Therefore, increased EZH2 expression in E7-expressing cells may be predicted to result in enhanced H1K26 methylation.

Epstein–Barr virus

The EBV is a human gamma-herpesvirus that predominantly establishes latent infection in B lymphocytes and epithelial cells. EBV is one of the most common viruses in humans. Ninety percent of the world's population is infected by it (Young and Rickinson 2004; Williams and Crawford 2006; Klein et al. 2007). EBV is associated with mononucleosis and with several human cancers such as Burkitt's lymphoma (BL; Bornkamm 2009), nasopharyngeal carcinoma (NPC), T- and NK-cell lymphoma, and gastric carcinoma (Fukayama et al. 2008). Moreover, EBV infection is involved in the etiology of several lymphoid and epithelial malignancies in immune-compromised humans, such as AIDS and posttransplant patients (Niller et al. 2008).

Double-stranded DNA genome of EBV viruses is huge, approximately 172 kb in size. In EBV infection, two stages can be distinguished, i.e., lytic and latent. During lytic life cycle, viruses are produced and finally released from the infected cells and viral genome remains as an episome in the host cell (Young and Rickinson 2004; Gatza et al. 2005; Williams and Crawford 2006; Klein et al. 2007). During latent infection, viral particles are not produced and several viral proteins called "latent proteins," which have oncogenic activity, are expressed. The latency state is regulated by six EBV nuclear antigens EBNAs: 1, 2, 3A, 3B, 3C, and LP; three latent membrane proteins LMPs: 1, 2A, and 2B; BARF-1 protein; two small RNA molecules: EBER 1 and EBER2; and BART RNA transcripts. Additionally, EBV codes for at least 20 miRNAs that are expressed in latently infected cells (Tao et al. 1998; Klein et al. 2007; Bornkamm 2009). EBV genome also encodes for: immediate genes (probably responsible for the switch between latent and lytic cycle), the early genes (e.g., enzymes influencing the host cell nucleotide metabolism and DNA synthesis), and the late gene products (e.g., the virion structural proteins; Young and Rickinson 2004; Gatza et al. 2005; Williams and Crawford 2006; Klein et al. 2007).

The important role in carcinogenesis of all EBV positive tumors but Burkitt's lymphoma, which is driven by the cMYC translocation, is played by LMP1 protein. LMP1 is one of the major EBV oncoprotein, which controls cell growth and promotes metastasis, apoptotic resistance, and immune modulation (Arvanitakis et al. 1995; Martin and Gutkind 2008). During B lymphocytes transformation LMP1 activates cell signaling pathways such as NFκB, inducing the expression of various genes that encode anti-apoptotic proteins and cytokines (Young and Rickinson 2004). LMP1 acts as a constitutively active receptor that mimics activated CD40, a member of the tumor necrosis factor family (Mosialos et al. 1995; Martin and Gutkind 2008). Critical role in EBV-induced transformation plays interaction between cytoplasmic carboxyl terminus of LMP1 and tumor necrosis factor receptor-associated factor and the tumor necrosis factor receptor-associated death domain protein (Brown et al. 2001). These interactions induce the activation of several key signaling molecules such as PI3K, JNK, and JAKs leading to the activation of transcription factors including NFκB, AP-1, and STATs (Kilger et al. 1998), which have been extensively related to human malignancies (Martin and Gutkind 2008).

In EBV-induced transformation as well as in EBV viral life cycle, epigenetic mechanisms such as DNA methylation and histone modifications, which control expression of latent viral oncogenes and miRNAs, play also an important role (Park et al. 2007b; Niller et al. 2008). Methylation of the EBV genome helps virus to hide from the host immune system, inhibiting expression of viral latency proteins that are recognized by cytotoxic T-cells (Robertson and Ambinder 1997; Paulson and Speck 1999; Tao and

Robertson 2003; zur Hausen 2006; Fernandez et al. 2009). Methylation pattern of EBV genome depends on the stages of EBV latency (0, I, II, III) and the type of tumor (zur Hausen 2006). It has been demonstrated that certain viral promoters of latent circular EBV genomes may undergo increased methylation (Niller et al. 2008). DNA methylation level in EBV genome increases dramatically from asymptomatic infection to final neoplastic stages and has been shown to be involved in regulation of viral genes expression. One of the EBV genes whose expression is epigenetically regulated is EBNA1. EBNA1 protein plays crucial function in viral replication and episome maintenance in latency. Expression of EBNA 1 is controlled by four promoters; Cp, Wp, Qp, and Fp (Tao et al. 1998). DNA methylation of these promoters regulates the expression of EBNA1 and eventually defines the type of latency stage. CpG methylation downregulates gene expression and induces the alternative transcription of EBNA1 from various promoters during the different latency stages which, at the same time, are associated with the pathology that the virus induces from a simple infection to a lymphoma and carcinoma (Li and Minarovits 2003; Yoshioka et al. 2003; Niller et al. 2008). Wp, Cp, and X promoters have been found to be methylated in I and II latency type in BL, Hodgkin disease (HD), and NPC cells. Interestingly, Qp promoter remains unmethylated independently of its activity. It is suggested that it might be regulated by a putative repressor protein and specific histone modifications (Tao et al. 1998; Li and Minarovits 2003; Fejer et al. 2008; Fernandez et al. 2009).

Epigenetic mechanisms are also used by EBV virus to initiate lytic cycle and replication. This reactivation is initiated by the expression of the immediate-early BZLF1 gene, which encodes for the transcription activator Zta. This protein has the ability to bind to methylated sites and activate the expression of the remaining lytic genes, thereby inducing a lytic infection (Bhende et al. 2005; Countryman et al. 2008; Dickerson et al. 2009; Heather et al. 2009). DNA methylation also modulates expression of LMP2A in BL, HD, and NPC, but has no affect on the expression of major EBV oncogenic protein LMP1 (Young and Rickinson 2004). Analysis of CpG methylation pattern in EBV genome showed that only five promoters do not possess the DNA methylation mark: EBER1, EBER2, Qp, BZLF1, and LMP2B/LMP1 (Fernandez et al. 2009).

Expression of many tumor suppressor genes involved in the cell-cycle control, apoptosis, intracellular signaling, proliferation, and surface adhesion might be downregulated by DNA hypermethylation induced by EBV viral proteins. It has been demonstrated that LMP1 oncoprotein induces the activation of DNMT1 leading to an increase in methylation of tumor suppressor genes promoters in nasopharyngeal carcinoma cells (Tsai et al. 2002; Niemhom et al. 2008). Moreover, reduction of E-cadherin expression is the result of LMP1-induced hypermethylation by activation of DNA methyltransferases DNMT1 3A and 3B. (Tsai et al. 2002). Besides E-cadherin promoter, other tumor suppressor gene promoters such as RASSF1, retinoic acid receptor, β2, p16 ^{INK4}, and p14 are also hypermethylated in NPC cells (Lo et al. 2001; Lo et al. 2002; Kwong et al. 2002; Tong et al. 2002; Pai et al. 2007). Similarly, LMP2A protein intermediates in the activation of DNMT1 that leads to downregulation of PTEN gene expression in gastric carcinoma cells (Hino et al. 2009). Expression of host genes might also be affected by viral Zta protein which downregulates early growth response 1 which is a cellular transcription factor involved in diverse biological functions such as cell proliferation, apoptosis, and differentiation (Chang et al. 2006).

EBV oncoproteins might also interact with components of histone modification machinery. EBV viruses possess the ability to change histone modifications and chromatin structure. EBNA 2 and 3c alter histone acetylation by interaction with p300/CBP complex or with HDAC, respectively (Wang et al. 2000; Knight et al. 2003). Interestingly, all oncoproteins which interact with epigenetic regulators are latent genes which are not typically expressed in BL, gastric cancer, and most nasopharyngeal carcinomas (Flanagan 2007). Latest reports have demonstrated that LMP1, similar to HPV16 E7 oncoprotein, upregulate the expression of KDM6B demethylase (specific for H3K27me3) in Hodgkin's lymphoma. It has been suggested that aberrant expression of KDM6B stimulated by LMP1 may contribute to the pathogenesis of HL. Moreover, the authors suggest that the changes in the distribution of the H3K27me3 mark, along with the dynamics of DNA methylation on early viral promoters, might also play a role in the latent/lytic switch (Anderton et al. 2011).

It has also been demonstrated that histone modifications play significant role in the activity of EBV promoters and expression of viral proteins (Gerle et al. 2007; Countryman et al. 2008; Fejer et al. 2008). Histone H3 lysine 4 dimethylation (H3K4me2) has been associated with Qp promoter activity and modulation of LMP2A expression. Acetylation of histone 3 and 4 has been linked with Qp, Cp promoter activity, and BZLF1 and LMP2A expression (Fernandez and Esteller 2010; Gerle et al. 2007; Countryman et al. 2008; Fejer et al. 2008).

EBV is the first virus that was reported to express miRNAs (Pfeffer et al. 2004). More than 20 miRNAs are encoded by EBV genome. They are differentially expressed in different phases of the viral life cycle and between the types of latency (Cai et al. 2006). EBV encoded miRNAs regulate both host and viral genes and have also been suggested to be implicated in the oncogenic properties of the virus (Pfeffer

et al. 2004; Nair and Zavolan 2006; Gottwein and Cullen 2008; Takacs et al. 2010; Moens 2009).

Kaposi's sarcoma-associated herpesvirus

KSHV also known as human herpesvirus 8 likewise EBV belongs to the *Herpesviridae* family. KSHV is associated with Kaposi sarcoma, one of the most common cancer in human immune deficiency virus-infected patients, primary effusion lymphoma (PEL), and some type of multicentric Castleman's disease (zur Hausen 2006). Similar to EBV virus, KSHV is a dsDNA virus, whose infection persists for life and it posseses two phase in its life cycle, i.e., latent and lytic. Seven KSHV genes are closely associated with latency and have potentially oncogenic activity: LANA, vcyclinD, vFLIP (K13), Kaposin (K12), vIRF2 (K11.5), vIRF3 (K10.5), and LAMP (K15) (Areste' and Blackbourn 2009; Dourmishev et al. 2003; zur Hausen 2006) All of these proteins have the ability to maintain lytic phase and to control latent cycle replication. Replication and transcription activator (RTA) is encoded by ORF50 of the viral genome and is the lytic switch of KSHV (Sun et al. 1998). Methylation of RTA (ORF50) promoter is used by virus to maintain the latent cycle. The main latency protein LANA (latency-associated nuclear protein) which remains unmethylated during KSHV infection also supports maintenance of the latent cycle by the association with ORF50 promoter or binding cellular factors which normally interact with ORF50 (Lu et al. 2006; Pantry and Medveczky 2009).

It has been shown that KSHV may influence host DNA methylation. LANA protein has been demonstrated to associate with DNA methyltransferase DNMT3a, which results in repression of approximately 80 cellular genes, some of which are known targets of epigenetic inactivation in various cancers (Shamay et al. 2006). Association and relocalization of DNMT3a induced by LANA has an influence on methylation of the H-cadherin gene promoter. It has also been reported that LANA associates with the TGF-β type II receptor (TβRII) promoter and induces its methylation (Di Bartolo et al. 2008). Reduction of TβRII expression in PEL cells results in defective TGF-β signaling-pathway, which is important for preventing the development of tumors because it inhibits growth and promotes apoptosis (Di Bartolo et al. 2008). Another tumor suppressor, p16INK4a, is also found to be inactivated by promoter hypermethylation. However, it has not been proved that LANA participates in its downregulation.

KSHV oncoproteins also interact with other components of epigenetic machinery. LANA protein interacts with the DNA methyl-binding protein MeCP2, the mSin3 transcriptional repression complex, and the histone methyltransferase SUV39H1, thus enabling numerous roles in epigenetic gene regulation (Flanagan 2007; Li et al. 2000). LANA, RTA, K-bZip, and viral homologue of interferon regulatory factor encoded by ORFK9 interact with histone acetyltransferase complex p300/CBP and lead to reduction of its activity (Li et al. 2000; Hwang et al. 2001; Lim et al. 2001; Gwack et al. 2001, 2002; Pantry and Medveczky 2009). Moreover, miRNAs encoded by KSHV virus are also involved in epigenetic regulation and expression of oncogenes (Cai et al. 2006; Flanagan 2007; Samols et al. 2007).

Hepatitis B virus

HBV is a member of *Hepadnaviridae* family. Viruses that belong to this family cause acute and chronic infections of the liver resulting in cirrhosis, hepatitis B, and HCC (Beck and Nassal 2007; Seeger and Mason 2000; zur Hausen 2006). HBV and HCV are the main factors responsible for HCC development in humans worldwide (Cougot et al. 2005; Gurtsevitch 2008). HBV contains a double-stranded circular DNA genome of 3.2 kb and it replicates by reverse transcription from an RNA intermediate (pregenomic RNA), which is transcribed from covalently closed circular HBV DNA (Yokosuka and Arai 2006).

In contrast to HCV infection during HBV replication, epigenetic mechanisms such as DNA methylation or histone modifications play an important role. Almost completely unmethylated HBV genome occurs in the early stages of carcinogenesis (e.g., hepatitis and cirrhosis); whereas, HBV genome is more methylated in the established liver tumors, both in clinical samples as well as in cultured cancer cell lines (Fernandez et al. 2009). The presence of DNA methylation at the C and S genes is related to their lack of expression. Conversely, X gene that encodes for HBx protein remains unmethylated (Fernandez et al. 2009). HBx oncoprotein, which plays an important role in carcinogenesis, is also a key factor responsible for epigenetic alteration in viral and host genome (Jung et al. 2007; Park et al. 2007a; Zheng et al. 2009). HBx protein interacts with DNMT1 and has influence on its expression. Increased expression of DNMT1 induced by HBx inhibits the expression of tumor suppressor genes such as p16 and E-cadherin (Jung et al. 2007). Moreover, HBx directly interacts and regulates the expression of DNMT3a and DNMT3b which also modulates host genes expression (Park et al. 2007a; Zheng et al. 2009). The same mechanisms are used by HBx to control viral genome methylation pattern (Jung et al. 2007; Park et al. 2007a; Zheng et al. 2009). HBx has also been demonstrated to associate with components of histone modification machinery, such as CBP/p300 HAT and HDAC, thus influencing gene expression (Cougot et al. 2007; Shon et al. 2009; Zheng et al. 2009).

Adenoviruses

Human Adenoviruses are small DNA viruses with non-enveloped icohasedral capsid (Russell 2009). More than 50 human serotypes of adenoviruses have been identified and subdivided into groups A to F (Blackford and Grand 2009; Russell 2009). Adenoviruses mostly cause respiratory infections but a subset of them containing all subgroup A and B (e.g., Ad12) are capable of promoting undifferentiated tumors when injected into rodents (Graham et al. 1984; Täuber and Dobner 2001; for a comprehensive review, see Doerfler 2009). Nevertheless, role of adenoviruses in human carcinogenesis is still unclear. It has been suggested that adenoviruses might not cause human cancers due to the fact that adenoviral DNA was generally not detected in human tumor cells. However, latest data indicate that adenoviruses can establish a form of latency in some human cells (Garnett et al. 2009). Moreover, because adenoviral DNA has been detected in brain tumors (Kosulin et al. 2007) then potential involvement of adenoviruses in human carcinogenesis should be considered. It has been proposed that adenoviruses might perform "hit and run" transformation of human cells (Nevels et al. 2001). According to this hypothesis, cellular transformation may be caused by transient viral infection, and after establishing neoplastic state of the cell, viral DNA is not necessary for the maintenance of transformed cellular phenotype. Studies on Syrian hamster cells transformed by Ad12 have demonstrated that despite of the gradual loss of multiple copies of integrated Ad12 genomes from these cells, their oncogenic potential was still maintained (Doerfler 2009). The "hit and run" oncogenesis concept could explain the role of adenoviruses as etiological agents in tumors that lack any viral genes and proteins (Nevels et al. 2001).

Oncogenic properties of adenoviruses have been attributed mainly to the function of early region 1 (E1) which encodes Ad E1A and E1B oncoproteins (Täuber and Dobner 2001). Apart from E1A and E1B oncoproteins, proteins encoded by E4 region have also been proposed to be involved in cellular transformation. Early proteins E4-ORF3 and E4-ORF6 of adenovirus Ad5 have been shown to be able of replacing E1B function in transforming cells and to increase cellular transformation mediated by E1A and E1B as well (Täuber and Dobner 2001). Early viral proteins E1A and E1B act as transcriptional factors involved in the regulation of viral and cellular gene expression and have been demonstrated to interact with many cellular proteins including tumor suppressors, RB proteins, and p53, respectively (Endter and Dobner 2004; Martin and Berk 1998; Kosulin et al. 2007; Zheng 2010).

Epigenetic alterations such as changes in DNA methylation pattern of viral and host genome as well as histone modification have been extensively demonstrated to occur in adenovirus-transformed cells. It has been observed that integrated adenoviral (Ad12) genome in hamster tumor cells becomes de novo methylated, contrary to free viral DNA, which is never methylated de novo (Doerfler 1991a, b; 1996; 2009). Moreover, changes in methylation pattern of cellular genome were found in cells which have Ad12 DNA integrated into host genome. However, it is unknown whether changes in methylation profile of cellular genomes are induced by insertion of adenoviral DNA or just by insertion of any foreign DNA (Doerfler 2009).

Many studies have also demonstrated that adenoviral oncoproteins interact with components of cellular epigenetic machinery. These interactions are another example of functional convergence of oncoproteins encoded by adenoviruses and HPV viruses. For instance, E1A correspondingly to E7HPV16 protein associates with the DNMT1 and increases its activity (Burgers et al. 2007). Moreover, E1A similar to E6 HPV16 protein binds to and inhibits HAT proteins CBP and p300. It has been shown that interaction between E1A and CBP/p300 leads to reduction of histone H3 lysine 18 acetylation (H3K18ac; Horwitz et al. 2008; Ferrari et al. 2009). In addition, E1A also binds to several other cellular proteins such as GCN5, PCAF, and p400, which are involved in the regulation of chromatin structure (Lang and Hearing 2003; Fuchs et al. 2001; Horwitz et al. 2008; Ferrari et al. 2009). Recent studies have demonstrated that E1A function results in epigenetic reprogramming of the host cell. It has been shown that E1A binds in a time-dependent manner to promoter regions of diverse sets of biologically related cellular genes which causes genome-wide redistribution of RB proteins and CBP/p300 on promoters, hypoacetylation of H3K18 in these regions, and subsequent target genes repression, which results in transcriptional reprogramming of the cell (Ferrari et al. 2008). Furthermore, recent studies have demonstrated that function of adenoviral E4-ORF3 protein may also induce extensive epigenetic alteration in transformed cells. It has been shown that E4-ORF3 stimulates de novo H3K9me3 heterochromatin formation specifically at p53 target promoters, thus leading to an inhibition of p53 DNA binding and silencing of p53-target genes transcription (Soria et al. 2010).

HTLV-1

HTLV-1 is a complex retrovirus with a single-stranded RNA genome that is associated with multiple diseases including an aggressive clonal malignancy of mature CD4+ T-lymphocytes called adult T-cell leukemia/lymphoma (ATL). It is also responsible for causing chronic inflammatory disease called HAM/TSP for HTLV-1-associated myelopathy/tropical spastic paraparesis (Araujo and Silva

2006). At present, HTLV-1 is still the only known human retrovirus directly linked to oncogenesis. It is estimated that about 20 million people worldwide are infected with HTLV-1 (Proietti et al. 2005). In spite of this, ATL develops only in minority of HTLV-1-infected individuals. The risk of ATL in HTLV-1-infected people is estimated to be approximately 6.6% for males and 2.1% for females (Arisawa et al. 2000). The causative role of HTLV-1 in ATL etiology is well documented. ATL develops only in HTLV-1 carriers. Moreover, it has been shown that all ATL cells contain integrated HTLV-1 provirus.

In contrast to mechanisms typical for animal retroviruses, HTLV-1-mediated oncogenesis involves virally encoded proteins rather than insertional mutagenesis or capturing and activating cellular proto-oncogenes (Yoshida 2001, 2005; Matsuoka and Jeang 2007). The main transforming protein of HTLV-1 is Tax oncoprotein, but recent studies evidence that the basic leucine zipper factor (HBZ) also plays a role in this process (Matsuoka and Jeang 2007). It has been proposed that Tax protein is needed to initiate ATL transformation, and HBZ protein is involved in leukemia maintenance (Matsuoka and Jeang 2007). Although Tax protein is required for the virus to transform T-cells, its transcripts are detected in only about 40% of all ATLs. It has been demonstrated that Tax expression is silenced in ATL cells, which enables transformed cells to evade immunosurveillance (Koiwa et al. 2002; Takeda et al. 2004; Taniguchi et al. 2005; Matsuoka and Jeang 2007).

Tax protein contributes to the initiation of T-cell transformation through various mechanisms, by deregulating the function and expression of key cellular factors involved in cell growth and proliferation, apoptosis, DNA repair, and cell division (Matsuoka and Jeang 2007). It has been demonstrated that Tax protein associates with centrosomes, causing their amplification and as a consequence multipolar mitosis and aneuploidy. It abrogates DNA repair which contributes to clastogenic DNA damage in HTLV-1-infected cells. It is also responsible for inactivation of factors involved in DNA damage response, e.g., p53, thus contributing to suppression of apoptosis and senescence. Other reported mechanisms of Tax-mediated transformation include activation of cyclin-dependant kinases, NFκB, and Akt signaling which promote cell survival and proliferation of HTLV-1 infected cells.

Many studies report that Tax protein also influences host cell epigenetic machinery. It has been shown that Tax protein forms complex with the phosphorylated form of the cellular transcription factor pCREB that recruits the cellular histone acetyltransferases CBP/p300 to promote changes in chromatin architecture characteristic for transcriptional activation. This mechanism of Tax-mediated change in histone acetylation is used by HTLV-1 to activate transcription of viral genes from viral long terminal repeats LTR and is required for high-level transcription of the proviral DNA. Recent evidences also show that Tax interacts with BRG1 subunit of chromatin-remodeling complexes. This interaction leads to HTLV-1 nucleosome remodeling and is required for Tax transactivation.

It has also been demonstrated that Tax protein can recruit histone methyltransferase SUV39H1 to 5′LTR and induce H3K9 methylation whereby it modulates its own expression which plays a role in the regulation of viral latency (Kamoi et al. 2006).

Summary

The studies in characterizing the molecular mechanisms of viral-induced carcinogenesis provide increasing evidence for the importance of the interactions between viruses and host cells at the epigenetic level. It is now apparent that viral oncoproteins target the elements of cellular epigenetic machinery changing their expression and/or activity thus leading to alterations in the epigenetic state of the host cell. Viral-encoded oncoproteins exploit specific epigenetic processes to force normal quiescent cells to replicate as well as to regulate viral genes expression during infections. DNA methylation in viral promoters modulates viral genes expression and is the mechanism used by many oncoviruses to avoid detection by the host immune system.

Epigenetic alterations in DNA methylation and histone modifications, leading to aberrant profiles of gene expression, are highly conserved function in tumor-associated viruses belonging to distinct evolutionary groups. Common targets for the viral oncoproteins are DNA methyltransferases (maintenance DNA methyltransferase, DNMT1, and/or de novo DNA methyltransferases, DNMT3a, DNMT3b) and histone-modifying enzymes, such as HDAC, HAT, histone methyltransferases, and demethylases. Emerging data also point toward a role of miRNA in the regulation of viral life cycle and pathogenesis of several virus-associated cancers. However, while changes in DNA methylation pattern and some histone modification changes induced by viral infection are better recognized, the function of miRNA still remains poorly understood.

The fact that oncovirus-induced epigenetic alterations within host cell during carcinogenesis are also a characteristic for most non-viral cancers demonstrates the similarity between the viral and tumor cell programs at the epigenetic level. Aberrant methylation patterns are an important and frequent event both in virus-associated and non-viral cancers (Robertson 2001; Jones and Baylin 2002). Many studies demonstrate an essential role of elevated Dnmt1, Dnmt3a, and Dnmt3b expression and activity in the development of cancers (Robertson 2001; Esteller 2006). The resulting hypermethylation of CpG island promoter

observed in many cancers has been widely demonstrated to cause silencing of tumor suppressor genes. Aberrant histone modifications in particular histone acetylation, which lead to misregulation in gene expression, are also a characteristic feature of human cancer cells. Inhibition of p300/CBP histone acetyltransferase activity is observed in many non-viral cancers. The germline mutations of CBP are found in Rubinstein–Taybi syndrome, a developmental disorder characterized by an increased predisposition to childhood malignancies, e.g., solid tumors, leukemias, and lymphomas. Moreover, frequent somatic mutations of p300/CBP have been detected in breast, colorectal, and gastric carcinomas (Iyer et al. 2004). Altered expression and mutations of genes that encode HDACs have also been associated with carcinogenesis (Ropero and Esteller 2007 and references therein). Overexpression of individual HDACs has been detected in many different tumors, but there are also evidences that alterations that result in the loss of function of class I HDACs may also be associated with cancer development. It has been proposed that the loss of class I HDAC function could induce the hyperacetylation and activation of genes regulated by RB protein, thus leading to cell-cycle deregulation (Ropero and Esteller 2007). Aberrant histone methylation has also been widely demonstrated to contribute to carcinogenesis. Deregulation of H3K27 methylation caused by both increased and decreased activity of enzymes controlling H3K27 methylation is observed in many cancers, which demonstrates that precise balance of this methylation plays an important role in normal cell growth (Simon and Lange 2008; Martinez-Garcia and Licht 2010).

In light of the discussed significance of epigenetic mechanisms in tumorigenesis, oncogenic viruses can be seen as important players changing the function of cellular epigenetic machinery, thereby contributing to cancer development. The models of virus-induced epigenetic reprogramming may also apply to non-viral mechanisms of oncogenesis. Therefore, the results of studies aimed at complete understanding of the viral interference with the cellular epigenetic processes will have a powerful impact also on understanding of the epigenetic mechanisms involved in human non-viral carcinogenesis.

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