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Kaposi sarcoma-associated herpesvirus and host DNA methylation

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Abstract: DNA methylation is an epigenetic mode that controls gene expressions, genome stability, and chromatin structure. The methylation pattern of a host cell's genomes is tightly controlled but can be disrupted by viral infections, including Kaposi sarcoma-associated herpes virus (KSHV). KSHV establishes lifelong latent persistence in the host and causes endothelial and lymphatic tumors. To promote viral latency and tumorigenesis, KSHV manipulates host cell DNA methylation through multiple mechanisms. Viral factors such as latence-associated nuclear antigen (LANA), viral interferon regulatory factor 4 (vIRF4), and certain micrornas (miRNA) directly or indirectly inhibit DNA methyltransferase (DNMT), the enzyme responsible for controlling DNA methylation. This results in abnormal changes in host DNA methylation that support proliferation, inhibit apoptosis, and inhibit the lytic replication cycle. Restoring normal regulation of host cell DNA methylation represents a promising therapeutic approach for reactivating KSHV lytic replication, controlling persistent infection, and treating associated malignancies. Targeting the viral proteins and miRNAs responsible for dysregulating host DNA methylation may help overcome issues with current epigenetic therapies. A better understanding of interactions between KSHV and the host cell methylome will enhance selection of key therapeutic targets and strategies, advancing development of novel treatments for virus-associated cancers with limited toxicity or drug resistance.

Keywords: DNA methylation, Kaposi's sarcoma-associated herpesvirus (KSHV), epigenetic, histone modification, tumor suppressor gene, oncogene

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1 Introduction

Kaposi's sarcoma (KS), first described by Hungarian dermatologist Moritz Kaposi in 1872, is a complex vascular malignancy with a distinctive clinical and pathological presentation. Historically associated with elderly Mediterranean men, the advent of the HIV pandemic in the 1980s saw KS emerge as a prevalent cancer among Acquired Immune Deficiency Syndrome (AIDS) patients. A significant breakthrough in understanding KS pathogenesis came in 1994 with the identification of Kaposi's sarcoma-associated herpesvirus (KSHV), a gamma-herpesvirus linked to not only KS but also to two other malignancies: Primary effusion lymphoma (PEL) and Multicentric Castelman's disease (MCD). KSHV's role in oncogenesis is multifaceted, involving the manipulation of host cellular processes, including DNA methylation and histone modification, which are critical epigenetic mechanisms.

Epigenetics, the study of heritable gene expression changes without alterations to the underlying DNA sequence, plays a pivotal role in normal development and disease pathogenesis, particularly in cancer. DNA methylation, a well-studied epigenetic modification, involves the addition of a methyl group to DNA by methyltransferases (DNMTs), leading to gene silencing when it occurs in promoter regions. This review delves into the intricate interplay between KSHV and the host's epigenetic machinery, focusing on how the virus induces aberrant DNA methylation patterns that contribute to tumorigenesis.

We will explore the impact of KSHV on the methylation status of key tumor suppressor genes such as P16INK4A and TβR, as well as the methylation of oncogenes like AXL and LGALS1. The implications of these epigenetic changes on tumor development and the potential for targeted therapies will be discussed. Understanding the epigenetic landscape altered by KSHV infection is crucial for developing novel therapeutic strategies aimed at reactivating silenced tumor suppressor genes and/or inhibiting the oncogenic potential of hypomethylated genes.
This review will also consider the broader implications of KSHV-induced epigenetic changes, including the potential for differential methylation regions to serve as diagnostic and prognostic markers for KSHV-associated malignancies. By elucidating the mechanisms by which KSHV reprograms the host epigenome, we aim to contribute to the existing body of knowledge on KSHV pathogenesis and facilitate the development of more effective treatments for KS and related cancers.

1.1 KSHV

1872, Hungarian dermatologist Moritz Kaposi first described a tumor in elderly Mediterranean men, characterized by deep red or dark brown skin, ulcerated papules and nodular neoplasms, and named the tumor “idiopathic multipigmented dermatosarcoma”, Kaposi's sarcoma (KS). In the 1980s, with the HIV pandemic, Kapo's sarcoma became the most common cancer associated with Acquired Immune Deficiency Syndrome (AIDS). In 1994, Chang et al., identified a unique DNA fragment derived from gamma-herpesvirus in the tissue of an AIDS patient and named it Kaposi's sarcoma-associated herpesvirus (KSHV) (Moore & Chang, 1995). Numerous epidemiological investigations have shown that KSHV infection may cause three

types of malignant tumors, KS, Primary effusion lymphoma (PEL), and Multicentric Castelman's disease (MCD).

KSHV belongs to the gamma-herpesviruses (Chang et al., 1994), It particles have the typical characteristics of herpes viruses, that is, double-stranded DNA viruses inside the envelope。 The KSHV DNA genome consists of terminal repeats (TRs) rich in GC sequences and a central long unique region (LUR). LUR encodes more than 90 open readingframes (ORFs), 12 precursor micrornas (pre-miRNA) and several non-coding RNA (ncRNA) (Mesri et al., 2010). In the genome of the herpes virus, 75 ORFs are highly conserved, named ORF1 to ORF75; KSHV also encodes 15 unique viral proteins, denoted by the prefix K, named K1 through K15. KSHV also encodes partially homologous and functionally similar proteins to host proteins, such as v-Cyclin, v-FLIP, v-IRF1, v-IL6, etc. These proteins participate in transcriptional regulation, anti-apoptosis, immune escape, cell cycle regulation and other signaling pathways. They play a pivotal role in the Latent infection establishing and promotes viral disease (Ganem, 2010; Mesri et al., 2010; Ueda, 2018).

Like other gamma-herpesvirus, there are two phases in the life of KSHV: the lysis stage and the latency stage. During the latency stage, the virus restricted the expression of a few viral genes, and no virions were produced; In the lysis stage, a large number of viral genes are expressed in a cascade according to a certain time sequence, and a substantial amount of mature viral particles are eventually produced and released after lysis of host cells. Both during the lytic and latent phases, viral genome replication occurs, facilitating long-term stable existence within the host organism (Mesri et al., 2010; Purushothaman et al., 2016). Under the induction of some factors such as sodium butyrate, KSHV can express a variety of lytic genes, such as ORF50 (lytic cycle switch gene), ORF26 and K8.1, and produce progeny virus particles (Sarid et al., 1998). When KSHV establishes latent infection in natural host cells, only latent genes like latent nuclear antigen-1 (LANA-1), viral cyclin, v-Cyc and other genes are expressed (Sarid et al., 1998). LANA-1 can effectively isolate and protect viral DNA during viral replication (Ballestas et al., 1999). Researche has confirmed that LANA-1 can adhere to and inhibit human tumor suppressor gene p53, thus affecting the apoptosis of infected cells (Friborg et al., 1999). v-Cyc, a viral homolog of cyclin D, can bind to human cyclin-dependent kinase 6 (CDK6), promoting cell cycle and uncontrolled cell differentiation (Swanton et al., 1997). The regulation of the replication cycle of KSHV may play a vital role in the occurrence or development of the disease. The virus enters the lytic phase, which is conducive to the virus escaping from the host cell attacked by the immune system, and thus immune escape occurs. Once these viruses have succeeded in latent infection, they express latent cyclin, leading to the transformation of the host cell.

2 Epigenetics and DNA methylation

The field of epigenetics studies heritable modifications in the expressions of the gene with no changing the DNA sequences. One of the most well-studied epigenetic modifications is DNA methylation, in which specific bases on a DNA sequence are converted by the methyltransferase (DNMT) to form S-adenosyl methionine (SAM) , A chemical modification

process in which SAM, as a methyl donor, obtains a methyl group by covalent bonding (Saxonov et al., 2006). DNA methylation is catalyzed by DNMT and usually occurs in gene promoters and repeating genome regions (Deaton & Bird, 2011). The DNA methylation system in mammalian cells consists mainly of three DNMTS: DNMT1, DNMT3A, and DNMT3B, DNMT1 is a major maintenance methyltransferase responsible for replicating methylation patterns during DNA replication, and DNMT3A and DNMT3B are de novo methyltransferases involved in the establishment of methylation patterns during early development (Jurkowska et al., 2011). Methylation of promoter regions is associated with gene silencing, while hypomethylation can lead to increased gene expression (Jones & Baylin, 2007). DNA methylation plays an important role in a variety of cellular processes, including embryonic development, genomic stability, and gene imprinting (Jeltsch & Jurkowska, 2014; Saxonov et al., 2006). Abnormalities in normal methylation patterns have also been linked to a variety of human diseases, including cancer (Rodriguez et al., 2008). The overall level of DNA methylation in the genome of most cancerous cells is reduced. Under the overall low methylation level, the hypermethylation of some tumor suppressor genes leads to gene silencing, which makes the growth and differentiation regulation of normal cells abnormal and the damage cannot be repaired in time, which is closely related to the formation of tumors. Many viruses have evolved mechanisms to manipulate host cell DNA methylation mechanisms to promote their own pathogenesis and establish lifelong persistent infection (Stuber et al., 2007).

3 KSHV infection and host gene methylation

It has been experimentally proven that KSHV plays a role in inducing host gene DNA hypermethylation, which might be a contributing factor to the development of virally induced malignancies. KSHV LANA binds to host chromatin by interacting with DNMT and enlisting DNMT3A (Shamay et al., 2006). In KSHV-infected cells, DNMT3A mRNA expression is increased, which may lead to inhibition of host gene expression (Sun et al., 2015a). KSHV vIL-6 can enhance the expression level and activity of DNMT1, resulting in overall DNA hypermethylation in endothelial cells.

Treatment of cells expressing vIL-6 via the 5-aza-CdR inhibits the abnormal cell proliferation and migration brought on vIL-6, suggesting that vIL-6 promotes host cell proliferation and migration by inducing hypermethylation of host DNA (Wu et al., 2014). Interestingly, it was also found that DNMT3B expression was down-regulated in KSHV-infected PEL cells (Journo et al., 2018a). In KS tissues, the expressions of DNMT1 and DNMT3A were up-regulated (Tso et al., 2018). Several viral proteins produced by KSHV can directly interact with and inhibit DNMT. Multiple KSHV miRNAs have been shown to directly or indirectly target DNMT transcripts and proteins (*Epigenetic Regulation of Kaposi's Sarcoma-Associated Herpesvirus Latency by Virus-Encoded MicroRNAs That Target Rta and the Cellular Rbl2-DNMT Pathway - PMC*, n.d.). Changes in the expression of these key methylation enzymes may be the main cause of host genome methylation. Abnormal DNA methylation in promoters leads to the oncogene activation or tumor suppressor gene silencing, which is closely related to the development of human malignant tumors (Jones & Baylin, 2007). After KSHV infection, some

host tumor suppressor genes are hypermethylated and the transcription level of tumor suppressor genes is reduced, and oncogenes are hypomethylated and the transcription level of oncogenes is upregulated, which ultimately leads to abnormal cell proliferation and apoptosis inhibition, which is conducive to the establishment of lifelong latent infection of KSHV and the promotion of tumor occurrence.

3.1 Methylation of the tumor suppressor gene P16INK4A

The tumor suppressant gene P16INK4A is situated upon human chromosome 9p21.3 with a total length of 815bp and has two introns and three exons. Its encoded P16INK4A protein is additionally referred to as cyclin-dependent kinase inhibitor 2A (CDKN2A), in the process of cell cycle regulation, P16INK4A protein competitively down-regulates CDK4 and CDK6 through the P16INK4A/Rb pathway, affecting downstream protein phosphorylation and preventing E2F factor from being activated, thereby preventing cells from entering the G1 phase into the S phase and participating in cell cycle regulation. Its inactivation can lead to hyperproliferation and cell cycle acceleration (Luo et al., 2018). Variants of the P16INK4A gene in human tumors are varied, including homozygous deletion, heterozygous deletion, intragenic base deletion, point mutation, and methylation. The 5 '-CpG fragment is the promoter region of P16INK4A, and its methylation inhibits the transcription of P16INK4A, resulting in the loss of P16INK4A protein expression. After demethylation, P16INK4A gene can be reactivated. P16INK4A gene is an important tumor suppressor gene. Except homozygous deletion and mutation, abnormal methylation of promoter region is the main mechanism of gene inactivation. Platt et al., (2022) found that there were hypermethylation changes in P16INK4A gene in KSHV-related tumors, which led to the silencing of P16INK4A expression and thus promoted the pathogenic effect of KSHV.

IL-6 is an important inflammatory factor, which can up-regulate the expression of DNMT1, lead to DNA methylation change, and promote the evolution of chronic inflammation to tumor. IL-6 induces abnormal DNA methylation in myeloma cells and bile duct cancer cells, and promotes tumor cell proliferation and invasion (Wehbe et al., 2006). IL-6 up-regulates DNMT1 expression and promotes abnormal changes in DNA methylation status of colorectal cancer cells (Foran et al., 2010). The amino acid sequence identity of vIL-6 and IL-6 is 24.8%, and they have similar biological functions (Moore et al., 1996). It was found that vIL-6 produced by KSHV can up-regulate the expression of DNMT1, lead to methylation of the promoter zone of tumors inhibits genes P16INK4A, then inhibit the expression of P16INK4A gene； The alteration of host DNA methylation induced by vIL-6 may be one of the tumorigenic mechanisms (WU et al., 2012). Uenogawa et al., (2011) found that the methylation of P16INK4A can be reversed with Azacitidine (AZA), a demethylating agent, which provides a potential new treatment method for tumors caused by tumor suppressor genes methylation.

3.2 Methylation of the tumor suppressor gene TβR

TGF-β receptor is encoded by the TβR gene, which is a transmembrane glycoprotein commonly found on the surface of normal cell-based tumor cells, mainly consisting of TβRI, TβRII and TβRIII subtypes (Sporn & Roberts, 1990). Various biological effects of TGF-β are mediated by their corresponding receptors. TGF-β signal transduction pathway mediates the function of cells growth inhibition, and the ligand receptors, Smads proteins and target genes of transcription regulation constituting this signal transduction pathway constitute a tumor inhibition pathway (Clark & Coker, 1998; Souchelnytskyi et al., 2001; Tzavlaki & Moustakas, 2020). The abnormality of any link in this pathway can lead to the disturbance of signal transduction, which leads to the occurrence and development of cancer. TβRII is an essential molecule in TGF-β signal transduction, performs an essential inhibitory function in epithelial cells growth, and is an important tumor suppressor gene. TβRII is localized to human chromosome 3p22 and is the initial transmitter of TGF-β anti-proliferation signal, and TβRII inactivation is common in human tumors. Reduced or absent TβRII results in the development of a variety of tumors, including non-small cell carcinomas。Hong-TaoZhang's teamdiscovered that abnormal methylation of TβRII gene 5'CpG in non-small cell lung cancer (NSCLC) tissues led to downregulation of TβRII gene at the transcriptional level, thus promoting disease progression(Zhang et al., 2004). Study has found that in KSHV infection-related diseases (including KS, PEL and MCD), LANA can cause downregulation of the expression of TβRII, thereby causing inhibition of TGF-β signaling pathway (Di Bartolo et al., 2008b). KSHV mediated TGF-β signal blocking influences the formation or progression of KSHV related cancers. In cultured tumor cells infected with KSHV, the TβRII gene promoter was found to be in a hypermethylated state, and after intervention with MS-275 and 5-azA-deoxycytidylate (5-aza-Dc), the expression of the TβR gene was upregulated.

3.3 Methylation of the cancer suppressor gene T-Cadherin/H-Cadherin (CDH13)

Ranscht and Ours -Zimmermann initially identified a distinct cadherin in chicken embryo brain matter in 1991. Because it does not encode cytoplasmic region, this truncated protein is called Truncatedcadherin. T-Cadherin (T-cadherin /H-Cadherin, CDH13) (Ranscht & Dours-Zimmermann, 1991). CDH13 is a novel cadherin molecule encoded by a single gene and located at locus 16q24 of the human chromosome (Lee, 1996). It was found that the expression of CDH13 mRNA was very high in normal tissues, but the hypermethylation of CDH13 gene and the silencing of CDH13 gene were detected in a variety of tumor tissues, furthermore the hypermethylation of CDH13 gene was significantly related with tumor invasion, recurrence and poor prognosis. Such as nasopharyngeal carcinoma, oropharyngeal squamous cell carcinoma, esophageal tumor, lung tumor, prostate tumor, bladder tumor, gallbladder tumor, endometrial tumor, ovarian tumor, breast tumor, melanoma brain metastases, cervical tumor (Bakkum-Gamez et al., 2015; Chen et al., 2016; Guo et al., 2016; Huang et al., 2015; Hutajulu et al., 2011; Kagohara et al., 2015; Millares et al., 2015; Siegel et al., 2015; van Kempen et al., 2014; L. Wang et al., 2014) and so on. Therefore, it is speculated that the inactivation of CDH13 may lead to tumor occurrence and invasion, and CDH13 may be a tumor suppressor gene. LANA can bind to the promoter of cadherin 13 (H-cadherin), then recruit DNMT3a to inhibit

CDH13 gene expression due to promoter hypermethylation (Shamay et al., 2006). Inhibition of H-cadherin expression will further promote the migration of cancer cells

3.4 Methylation of the tumor suppressor gene PDLIM2

Researchers identified PDLIM2 in a transcriptional cDNA library expressed in the iris corneal horn tissue of the rat eye (Loughran et al., 2005; Torrado et al., 2004) and named it Mystique (Loughran et al., 2005) or SLIM(Tanaka et al., 2005; Ungureanu & Silvennoinen, 2005). The PDLIM2 gene is situated on chromosome 8 (Loughran et al., 2005). Insulin-like growth factor 1 (IGF-1) and cell adhesion molecules promote the production of PDLIM2. PDLIM2， called as Mystique, is an IGF-1 receptor connector protein localized on the actin cytoskeleton which is required for epithelial cell migration (Loughran et al., 2005). PDLIM2 controls the steadiness and activation of transcription molecules like NF-κB, STATs, and β-catenin, thereby playing a role in tumor, immunology, and inflammation. PDLIM2 acts as a cancer-inhibiting factor in several tissues, and in tumors of lung, breast, ovarian, and other tissues, it often undergoes genetic mutation or epigenetic silencing (Guo & Qu, 2021). PDLIM2 gene plays a role in tumor inhibition in a variety of malignant tumors (Qu, et al., 2010; Qu, et al., 2010; Sun et al., 2019). A research has found that the down-regulation of PDLIM2 expression at the transcriptional level in colon cancer is closely related to the hypermethylation of the PDLIM2 gene promoter region (Qu, Yan, et al., 2010). The expression of PDLIM2 is sufficient to inhibit the anchor-free proliferation of malignant cells in vitro or tumor formation in vivo, so it is recognized as a tumor suppressor gene (Guo & Qu, 2021). KSHV inhibits the expression of PDLIM2 from the beginning phase of tumorigenesis, and the down-regulation of PDLIM2 expression is crucial to the sustained initiation of NF-κB and STAT3 induced by KSHV, as well as tumorigenesis and tumor maintenance. Inhibition of PDLIM2 transcription by KSHV is related to DNA methylation inside the promoter area, and this inhibition can be turned around by 5-aza-2-deoxycytidine and vitamin D (Sun et al., 2015b). This finding offers novel treatment options for KSHV-mediated malignancy in addition to advancing our knowledge of the pathophysiology of KSHV.

3.5 Methylation of the oncogene AXL

The AXL, situated on chromosome 19q13.2, consists of 20 exons that together encode a protein molecule of 894 amino acids. For the first time in patients with chronic myeloid leukemia (CML) chronicmyelogenousleukemia, was found in, is made up of AXL genes encode proteins, called AXL (UFO, ano, Tyro7, JTK11). The AXL gets its name from the Greek anexelekto, which means “uncontrolled” and is a member of the TAM (TYRO3-AXL-MER) familyAXL gets its name from the Greek anexelekto, which means “uncontrolled” and is a member of the TAM (TYRO3-AXL-MER) family. (Graham et al., 2014). The AXL includes three parts: extracellular domain, transmembrane domain, and intracellular domain. AXL ligand to stunted growth specificity protein 6 (growtharrestspecificprotein6 Gas6). The activation modes of AXL include ligand-dependent activation and ligand-independent activation. Studies have found that AXL activation is related to NF-κB, MAPK, PI3K, PKB and S6K signaling pathways, AXL is overexpressed in lung adenocarcinoma, breast cancer, pancreatic cancer,

gastric cancer and other tumor tissues, AXL plays a complex role in tumor biology. These include promoting tumor cell growth, invasion, metastasis, and resistance to angiogenic therapies (El-Khoueiry et al., 2021; Tsukita et al., 2019; Zhu et al., 2019). The development of small molecule inhibitors and antibodies targeting AXL is one of the hot topics in the field of tumor therapy. AXL is highly expressed in the endothelial cell infected with KS and KSHV, and the gene promoter was hypomethylated in cells cultured in vitro. The high expression of AXL in KS cells may be related to the hypomethylation of gene promoter. The induction of receptor apoptosis by Mab173 also inhibited the invasion of KS cells, and proved that the antibody can reduce tumor growth, increase tumor cell apoptosis, and significantly reduce AXL protein level in tumors (Liu et al., 2010). AXL gene is expected to be a target therapy site for KS.

3.6 Methylation of the oncogene LGALS1

Galectin-1, the protogalectinoid of homodimers, is encoded by the LGALS1 gene located on human chromosome 22q13.1 (Shaikh et al., 2020). Involved in multiple biological processes in the human body, including cell differentiation, tissue development, mRNA splicing, immune regulation, and tumor progression (Bogut et al., 2023). Galectin-1 is highly expressed in multiple tumor types, including lung, stomach, colorectal, and bladder carcinoma, furthermore, is linked with bad prognosis or metastasis, according to various studies. (Corral et al., 2022; Peng et al., 2021; Zheng et al., 2023; Zhou et al., 2021). Upregulation of Galectin-1 contributes to tumor growth and promotes tumor progression by regulating cell motility (Pucci et al., 2021), inducing activated T cell apoptosis (*The Role of Tumor Microenvironment in the Pathogenesis of Sézary Syndrome - PubMed*, n.d.), mediating cell adhesion (*Galectin-1 Influences Breast Cancer Cell Adhesion to E-Selectin Via Ligand Intermediaries - PubMed*, n.d.), and participating in tumor angiogenesis (Abu El-Asrar et al., 2020). Upregulation of Galectin-1 contributes to tumor growth and promotes tumor progression by regulating cell motility, inducing activated T cell apoptosis, mediating cell adhesion, and participating in tumor angiogenesis. Upregulation of LGALS1 was detected in KSHV-infected cells (Wang et al., 2004). In KS mouse models, reduction in Galectin-1 activities reduces angiogenesis and carcinogenesis (Paz et al., 2001). Genome-wide methylation analysis of Virus infected cell models and PEL cells showed that several gene promoters were hypomethylated and down-regulated, including LGALS1 gene (Journo et al., 2018b). Therefore, LGALS1 gene is expected to be a potential biomarker of KSHV-related malignancies.

3.7 Methylation of other genes

In order to comprehensively understand DNA·methylation status in KSHV-infected cells, Guy’s team conducted genome-wide methylation analysis of Virus infected cell models and PEL cells by using a whole genome methylation chip combined with high-throughput RNA sequencing analysis (Journo et al., 2018b). 215 genes with down-regulated promoter hypermethylation and 531 genes with up-regulated promoter hypomethylation were identified in PEL cells. Further analysis of three genes with hypermethylated promoters, DUSP10, EHD3, and CD40, showed that they were outstandingly inhibited in PEL cells, and all three genes were

reactivated after treatment with the demethylating agent 5-AZA-dC. Treatment with low dose of 5-AZA-dC can effectively inhibit the growth of PEL cells. These findings support the possibility of using 5-AZA-dC for the intervention of PEL or KSHV-associated infections

4. Targeted therapy strategies based on host genome methylation abnormalities

Since DNA methylation is maintained by DNMT, using DNA methyltransferase inhibitors to reverse the hypermethylation of tumor suppressor genes has become an effective clinical treatment strategy based on the abnormal methylation characteristics of tumor genome. At present, demethylation drugs mainly refer to DNMT inhibitors, which restore the function of tumor suppressor genes by inhibiting DNMT, so as to achieve the purpose of tumor treatment (Egger et al., 2004). At present, the FDA has approved drugs 5-azacytidine (azacytidine) and 5-azaza-2-deoxycytidine (decitabine), which as inhibitors of DNMTs, can play a demethylation activity at low doses, so as to play a role in the treatment of myelodysplastic syndrome and leukemia (Chuang et al., 2010; Koch et al., 2018). A study showed that the treatment of 4 tumor cell lines with 5-aza-CdR induced the re-expression of P16INK4A gene in 3 tumor cell lines, which inhibited the growth of tumor cells. It was also found that emodin combined alongside 5-aza-CDR promoted the demethylation of 5-aza-CDR on p16, RASSF1A and ppENK through decreasing DNMT1 or DNMT3a (PAN et al., 2016). In human bladder cancer, the tumor suppressive effect of 5-aza-CDR maybe due to the reactivation of silenced RASSF1A by changing the DNA methylation state of the gene (Liu et al., 2009). After treatment with 5-aza-CDR, the methylation of the promoter region of the tumor suppressant gene RASSF1A was reversed from methylation to non-methylation, thus playing a role in the treatment of cholangiocarcinoma (Zuo et al., 2007). Studies have shown that 5-aza-CdR is able to reactivate methylated TβRII gene expression in diseases where KSHV infection occurs (Di Bartolo et al., 2008a). Journo et al., (2018b) also found that after 5-AZA-dC treatment, the down-regulated expressions of LGALS1, DUSP10, EHD3 and CD40 induced by KSHV could be reactivated, effectively inhibiting the growth of PEL cells. Therefore, the reversal strategy of abnormal methylation may be a new approach for KS treatment.

5 Conclusion

CpG dinucleotides is an epigenetic mark. KSHV infection changes the CpG methylation status in host cells, resulting in hypermethylation and reduction of tumor suppressor genes, hypomethylation and up-regulation of oncogenes, which may be an important mechanism of KSHV-induced tumorigenesis. Differential methylation regions of KSHV-infected and uninfected cells can also serve as the basis for important markers of cancers linked to KSHV. Tumor development may be inhibited by actions that change the methylation profiles of these malignancies. However, the current research on the relationship between tumor suppressor genes, oncogenes and KSHV-infected tumors is not deep enough, which restricts the prevention, diagnosis and treatment of KSHV-related diseases. Interestingly, although the epidemiological relationship between KSHV and KS has been established, the incidence of KS in people infected only with KSHV is not high, and 20% of AIDS patients in North America are co-infected with KS(Li et al., 2017), indicating that HIV-1 is a potential and important

cofactor in the pathogenesis of KSHV. Determining whether HIV-1 influences the replication cycle of KSHV to promote tumor occurrence by manipulating host gene methylation status can provide theoretical basis for revealing the molecular mechanism of AIDS-KS pathogenesis.

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