Chapter 9

The Involvement of Epigenetic Mechanisms in HPV-Induced Cervical Cancer

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Additional information is available at the end of the chapter

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Abstract

High-risk human papillomavirus (HPV) genotypes infection associates with cervical dysplasia and carcinogenesis. hr-HPV transforming potential is based on E6 and E7 viral oncoproteins actions on cellular proteins. A persistent infection with hr-HPV leads to progression from precursor lesions to invasive cervical cancer inducing changes in host genome and epigenome. Pathogenesis and development of cancer associated with both genetic and epigenetic defects alter transcriptional program. An important role for malignant transformation in HPV-induced cervical cancer is played by epigenetic changes that occur in both viral and host genome. Furthermore, there are observations demonstrating that oncogenic viruses, once they integrated into host genome, become susceptible to epigenetic alterations made by host machinery. Epigenetic regulation of viral gene expression is an important factor in HPV-associated disease. Gene expression control is complex and involves epigenetic changes: DNA methylation, histone modification, and non-coding RNAs activity. Persistent infection with hr-HPV can cause viral DNA integration into host genome attracting defense mechanisms such as methylation machinery. In this chapter, we aim to review HPV infection role in chromatin modification/remodeling and the impact of HPV infection on non-coding RNAs in cervix oncogenesis. The reversible nature of epigenetic alterations provides new opportunities in the development of therapeutic agents targeting epigenetic modification in oncogenesis.

Keywords: HPV, epigenetic regulation, DNA methylation, histone modification, ncRNAs

1. Introduction

Cervical cancer accounts for almost 12% of all cancers in women, representing the second most frequent gynecological malignancy in the world, human papillomavirus (HPV) being considered as etiologic agent of this malignancy [1, 2]. HPVs exhibit tropism for skin or mucosal epithelium where they cause warts, benign lesions that usually regress. HPV prevalence is a combination of incidental and persistent infections that have accumulated over time, due to lack of clearance. Infection with a high-risk HPV (hr-HPV) type is considered necessary for the development of cervical cancer, but by itself, it is not sufficient to cause cancer [3, 4].

The persistent infection with hr-HPVs that have tropism for mucosal epithelia has been defined as the cause of more than 98% of cervical carcinomas as well as a high proportion of other cancers of the anogenital region (vulvar, vaginal, and penial) and oropharyngeal region [5]. It is known that persistent infection with hr-HPV genotypes is necessary but not sufficient for the development of high-grade cervical lesions and progression to malignancy. Persistent infection is characterized by continuous detection of the virus or its intermittent detection, due to latency, although the mechanism of latency has not yet been established but it is clear that the differences between active and latent cervical infection are qualitative and/or quantitative. The high prevalence of HPV infection in precancerous and cancerous cervical lesions confirms its oncogenic potential, different genotypes seem to be responsible for invasive cancer development. Approximately, 40 HPV genotypes were found to be associated with anogenital infections and are generally classified according to their oncogenic potential into low-, high-, and intermediate-risk types. High-risk or oncogenic types such as HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are considered so due to their presence in high-grade squamous intraepithelial lesions (HSIL) or cervical cancer [6]. hr-HPV genotypes 16 and 18 are causing more than 70% cervical cancer cases and most of the anogenital cancer as well as oropharyngeal tumors in men and women.

The molecular mechanism of cellular transformation induction involves epigenetic abnormalities along with genetic alterations. HPV disrupts normal cell-cycle control, promoting uncontrolled cell division, and the accumulation of genetic damage. The transforming properties of hr-HPV E6 and E7 oncoproteins are in interaction with many host cell proteins resulting in the maintenance and the reentering into cell cycle, permitting the virus to replicate, as it is dependent on the host cell DNA replication machinery.

Both E6 and E7 oncoproteins are able to interfere with key cellular processes (cell cycle, senescence, apoptosis and telomere shortening, differentiation). Furthermore, because of the frequent integration of the hr-HPV genome into a host cell chromosome, those two proteins are the only viral proteins known to be consistently expressed in HPV-associated cancers [7, 8]. Persistent infection with hr-HPV genotypes determines progression from precursor lesions to invasive cervical cancer by inducing changes in the host genome and epigenome. Transcriptional modification program through genetic and epigenetic alterations leads to cancer development. Gene expression control is complex and involves epigenetic changes.

hr-E6 protein is one of the most studied HPV proteins due to its many functions and is found to be interacting with many host cell proteins. Although E6 protein leads to p53 protein loss,

an important element of cell transformation [9], many studies have identified a number of additional cellular targets that may play an important role. HPV E6 interferes with different apoptosis pathways by additional interactions with key mediators (TNFR-1, FADD, CASP8, BAK, DFF40, GADD34/PP1, and TIP60) [10–15]. E6 protein is found to interact with proteins involved in cell cycle, cell-cell contact and polarity (MUPPI, E6BP, MAGI 1/3, DLG, PAT, paxillin, interacts with many proteins directly involved in DNA repair such as BRCA1, XRCC1, and MGMT [16–24] and targets other cell proteins involved in chromosomal and DNA stability for instance NFX1, hTERT, MCM7 [25, 26]. The E6 protein appears to have role in immune evasion as it interacts with tyk-2 and IRF-3 proteins both of which are involved in interferon signaling [27, 28].

E7 protein key activity is to overcome tumor suppressor block controlled by the pRb family proteins (RB, p107, p130) through disruption of pRb–E2F complexes thereby initiating the E2F mediated transcription [29]. E7-pRB complex leads to functional inactivation and disruption of cell-cycle progression in S phase. Another E7 hr-HPV function is as cell-cycle regulator, in doing so, the oncoprotein binds to p21/p27 and subsequent inactivates the CDK inhibitors [29, 30] and also to cyclins A, E in order to regulate cell cycle through pRb, p107 binding [31, 32]. On the other hand, E7 is known to be involved in transcription modulation by targeting host cell proteins AP1, TBP, MPP2, E2F6, and Skip [33–37]. In addition, E7 hr-HPV protein binds to histone deacetylases (HDACs) in a pRb-independent manner, which promotes cell growth. The E7 protein can also associate, directly or indirectly, with histone acetyl transferases (HATs) (p300, pCAF, and SRC1) and abrogates SRC1 associated HAT activity [38].

Following persistent infections with hr-HPVs, E6, and E7 oncoproteins acts on the DNA and cause epigenetic changes. The cooperation between genetic and epigenetic alterations leads to the malignant phenotype and cancer progression. In contradiction to genetic alterations, the epigenetic changes are reversible, making them therapeutic targets in various conditions, and do not affect DNA sequence of the genes, but determine the gene expression regulation acting on the genome. It is well supported that cancers are epigenetically deregulated. Disruption of epigenetic processes determines altered gene function leading to imprinting disorders, developmental abnormalities and cancer. Epigenetic regulation of viral gene expression is an important factor in HPV associated diseases, due to processes that arise independently of changes in the underlying DNA sequence. Gene expression control is complex and involves epigenetic changes such as DNA methylation [39], histone modifications, and chromatin-remodeling proteins [40] and DNA silencing by non-coding RNAs (ncRNAs) [41].

Taking into account that molecular mechanism induction of cellular transformation involves epigenetic abnormalities along with genetic alterations, in this chapter, we aim to review: (1) DNA methylation and cervical cancer; (2) the role of HPV infection in chromatin modification/remodeling; (3) the impact of HPV infection on ncRNA in cervix oncogenesis; (4) epigenetic changes involved in viral gene expression; (5) potential epigenetic biomarkers in cervical cancer.

2. DNA methylation and cervical cancer

The most studied epigenetic mechanism is DNA methylation. DNA methylation is a general term for processes of DNA bases (adenine, cytosine, and guanine) change by addition of a methyl group. Methylation of DNA bases can be achieved either under physiological conditions after a specific endogenous enzyme reaction by transferring the methyl group from a donor (biological methylation), or non-physiological conditions through the action of chemical compounds: alkylating agents. DNA methylation plays an important role in various cellular processes including gene expression, silencing of transposable elements, as well as in the defense mechanism against viral infection.

In several types of cancer, many genes have been reported to be hypermethylated. DNA hypermethylation results in blocking of affected gene transcription, causing silencing them. In cancer, hypermethylation is considered one of the most important mechanisms for tumor suppressor gene silencing, responsible for the control of the normal cellular differentiation and/or inhibition of cell growth. The main chemical DNA modification is methylation of cytosine, commonly found in areas with CpG dinucleotides islands. Almost 60% of promoters of genes encoding proteins in the human genome contain CpG islands, and the majority are methylated in varying degrees, depending on the tissue [42].

Cytosine methylation is a stable inherited and reversible hallmark and is generally associated with transcriptional repression. The methylation inhibits transcription factors that bind to recognized DNA sequences by the recruitment of methyl cytosine binding protein (MECP and MBD) with corepressor molecules. The way that 5-methylcytosine (5-mC) repress transcription at the promoter level is by the recruitment of methyl binding proteins (MeCP2, MBD1, MBD2, MBD3, MBD4), which subsequently interacts with another protein to repress DNA transcription as well as HDAC and other chromatin remodeling enzymes [43].

DNA methylation is controlled by DNA methyltransferase (DNMT), which catalyses the transfer of the methyl group from S-adenosyl methionine donor (SAM). Three active catalytic DNA methyltransferases were identified as follows: DNMT1, DNMT3A, and DNMT3B.

First tumor suppressor gene identified as hypermethylated was pRB, and then was followed by multiple publications describing similar phenomena for a variety of tumor suppressor genes such as p16, MLH1, VHL, and E-cadherin [44, 45]. It remains controversial whether tumor suppressor gene hypermethylation is a cause or a consequence of silencing them. DNA methylation is reversible and various chemical compounds are known that can reactivate gene expression [46].

On the other hand, DNA hypermethylation may be a secondary process, due to changes in chromatin role in maintaining the status repression of gene expression. More evidence of this hypothesis, resulting from experiments showing that when DNA methyltransferase expression was blocked *in vitro*, histone H3K9 methylation determined silencing of p16 gene in the absence of promoter DNA methylation [47, 48]. It was shown in cervical carcinoma that tumor suppressor genes are silent or abnormal diminished expressed due promoter hypermethylation (**Table 1**).

Gene	Methylation percentage	Activity
DcR1/DcR2	100%	Apoptosis [50–53]
hTERT	57%	
p16	8–42%	Cell cycle control [54, 55]
p73	39%	
PTEN	58%	WNT pathway [56, 57]
E-cadherin	28–80.5%	
APC	11–94%	
MGMT	5–81%	DNA repair [58]
FANCF	30%	FA-BRAC pathway [59, 60]
BRACI	6.1%	
hMLH1	5%	DNA mismatch repair [61]
RASSF1A	0–45%	Ras negative effector [62]
DAPK	45–100%	Cell death/metastasis [63]
TSCLC1	58–65%	Tumor suppressor [64]
FHIT	11–88%	Cell death/repair [65, 66]
HIC1	18–45%	Transcriptional factor [55, 67]
RARβ	33–66%	Cell differentiation [68, 69]
TIMP2/TIMP3	47%	Metalloprotease inhibitors [70, 71]
Calveolina1	6%	Calveole membrane [72, 73]
ERα	25%	Estrogen receptor alpha [74]
miR124	59%	Tumor suppressor [75]
miR-34b	48%	
miR-203	57%	

Table 1. Hypermethylated tumor suppressor genes in invasive[R1] cervical cancer (Adapted with permission from Dueñas-González et al. [49]).

On the other hand, microRNA genes undergo methylation-mediated transcriptional repression in cervical cancer miR-149, miR-375, miR-432, miR-1286, miR-641, miR-1290, miR-1287, and miR-95 [75–77].

CADM1, MAL, PAX1, and ADCYAP1 genes promoter hypermethylation were found to be involved in HPV-mediated transformation and may be significantly associated with the development of cervical cancer [78].

It was shown that hTERT, mir124-2, and PRDM14 were the first genes that became methylated during experimental immortalization. Following immortalization, ROBO3 methylation and CYGB was methylated, followed by CADM1, FAM19A4, MAL, PHACTR3, and SFRP2 [79].

3. The role of HPV infection in chromatin modification/remodeling

Nucleosomes are the basic repetitive units of chromatin and are intended to pack huge eukaryotic genome in the nucleus (mammalian cells contain approximately 2 m linear DNA packed into a nucleus-sized 10 mm diameter). Nucleosomes are further compacted to form chromosomes. These structures confer DNA compaction, but also create a base for the gene expression regulation. Nucleosome core particle is approximately 147 base pairs wrapped around a histone octamer made up of two copies of the histones H2A, H2B, H3, and H4.

Histone H1 (linker histone) and its isoforms are involved in chromatin compaction and underlying nucleosomes condensation. Compaction of chromatin in the cell nucleus is necessary but is not fully understood. In nucleosomes compacting DNA linker—10 nm has an important role. A chain of nucleosomes can be arranged in 30 nm chromatin fibers whose formation is dependent of histone H1. A 30-nm chromatin fiber is arranged as a loop around a central protein scaffold to generate the active form of the transcription-euchromatin. Compacting the fibers can lead to transcriptionally inactive form—heterochromatin [80].

3.1. Histone modifications

Covalent modifications of histones (epigenetic changes) are regulatory elements important in many biological processes. They affect chromatin interactions by structural changes in the histones or by modifying the electrostatic interactions and non-histone proteins recruit [81]. Histones can undergo a variety of post-translational modifications at the N-terminus, which is represented by acetylation, methylation, phosphorylation, sumoylation, ADP–ribosylation, and ubiquitination. They can alter the DNA histone interaction, with a major impact on chromatin structure. Some covalent modifications of histones are involved in transcription and are associated with DNA repair process. On the other hand, the phosphorylation of histone H2AX appears to be unique modification in DNA repair. Histone modifications may influence both among themselves and in interaction with methylated DNA, and the presence of numerous changes in the combined space-time context creates a program of genome expression profile specific to each cell to keep identity.

3.2. Histone acetylation

Histone acetylation is a modification of the lysine aminoacid that neutralizes the positive charges occurring at specific targets of nucleosome core. It has been speculated that histone acetylation can alter DNA interaction, helping to create more open chromatin architecture. Acetylation of lysine residues is catalyzed by HATs by transfer of an acetyl group from acetyl-coenzyme A to ε nitrogen of the lysine aminoacid. With few exceptions, these changes tend to create a relaxed form of chromatin, open for transcription, while deacetylation performed by HDACs is associated with transcriptional repression. Many transcriptional activators have been identified possessing intrinsic activity acetyl transferase: Gcn5/PCAF, CBP/p300, and SRC-1. Similar to these co-activators that exhibit HAT activity, there are co-repressors with HDAC activity, such as mSin3a, NcoR/SMRT and NURD/Mi-2 [82]. Rpd3 complex is an exception, being a complex with HDAC activity, associated with the active form of RNA polymerase II. Through this association is Rpd3 complex transcriptional repressor of initiation [83].

3.3. Histone methylation

Methylation of H3 and H4 histone at lysine and arginine residues arises in mono-, di-, or tri-methylated form and is conducted using a specific histone methyltransferase (HMT) that acts at the level of these residues. HMTs can catalyze the addition of up to three methyl groups on the ε nitrogen of lysine [84]. Co-activators, such as arginine methyltransferase (CARM1) and

protein arginine methyltransferase (PRMT1), are essential for histone H3 and H4 arginine methylation [85]. Most of HMTs contain catalytic domains, named SET conserved domains named after *D. melanogaster* Su (var)3-9 Enhancer of Z-(E(z)) and trithorax (TRX), although there are some exceptions of HMTs without SET domain [85–88]. H3K4 and H3K36 methylation is carried out by several methyltransferases. This redundancy makes the study of histone methylation more complex. Mammalian H3K79 methyltransferases include Suv39h1,2, G9a, and ESET [89]. EZH2 catalyses methylation of histone H3K27 and PR-Set2 (also known SET 8) with Suv4-20h1,2 catalyzes histone H4K20 methylation [90]. Methylation of H3K9, H3K27, and H4K20 is generally linked to the formation of heterochromatin in the presence of a transcriptional repressor HP1, while methylation of H3K4 and H3K36 is associated with transcriptionally active regions [91]. Methylation of histones lysine is reversible, being made by two enzymes families: aminooxidases (LSD1) and hydroxylases (JmjC family members), which may also demethylate trimethylated lysine [92, 93]. It was identified a series of proteins that bind to post-translationally modified histones. For example, methylated lysine residues can bind to protein with conserved regions, like plant-homeodomain (PHD) and chromodomain (CHD), whereas acetylated lysine residues bind to proteins with bromodomain [94]. These recruitment and recognition events can serve as a regulatory mechanism for other mechanisms that lead to other modifications of the histones. Two main complexes were identified, accompanying epigenetic changes, and containing members of trithorax (TrxG) and Polycomb (PCG) group. Some components of complex PCG and TrxG exhibit histone–methyltransferase activity, while other members interpret histones modifications playing a central role in gene regulation, coordinating such DNA availability for development and to establish cell faith. This are accomplished by pausing the state of balance between silent transcriptionally heterochromatin (PCG) and competent transcriptionally euchromatin (TrxG) [95].

3.4. Histone phosphorylation

Histones are phosphorylated at specific sites (serine residues) during cell division [96]. Phosphorylation process requires certain kinases. All four histone suffer phosphorylation; their biological meanings depend on the context. For example, histone H4S1 is evolutionary conserved role in chromatin compaction during the late stages of gametogenesis [97]. Phosphorylation of histone H2A (human—Ser14 in yeast—Ser10) is correlated with meiotic chromosome condensation, but disappears during meiotic division [98]. Chromatin condensation in apoptosis has been linked to the phosphorylation of histone H2B, in both humans and yeast. Histone phosphorylation seems to have a role in transcription. It was shown that phosphorylation of histone H3 determines the competence of transcriptional response for JUN and FOS genes immediately. These changes occur due to activation of Ras-MAP kinase pathway by growth factors.

3.5. Histone ubiquitination

Ubiquitin is a polypeptide that is attached covalently to other proteins as a result of a steps series involving activation and conjugation enzymes of ubiquitin E1 (ubiquitin activating

enzyme), E2 (ubiquitin conjugating enzyme) and ubiquitin ligase (E3) [99]. Polyubiquitination or more ubiquitin molecules addition to a protein is a classic signal for degradation via the proteasome. Histone H2A was first protein identified to serve as ubiquitin substrate [100]. Histone ubiquitination may be reversible using deubiquitinases. Like histone acetylation, ubiquitination is important in regulating gene expression. Highly ubiquitinated histones H2A and H2B have been associated with transcriptionally active sequences. Removing the ubiquitin residues on histone H2A leads to transcriptional repression [101].

3.6. ADP-ribosylation

ADP-ribosylation is a post-translational modification of proteins, including histones, which involves the addition of one or more residues of ADP and ribose. Mono or poly ADP-ribosylation is mediated by MARTs (Mono-ADP-ribosyltransferases) or PARPs (poly-ADP-ribose polymerases) enzymes [102]. ADP-ribosylation of histones is carried out in a single-site H2BE2ar1 [103]. Recently it was demonstrated the role of PARP-1 in transcriptional activity, but only if that DNA repair process was induced [104].

3.7. Crosstalk between DNA methylation and histone modifications

Several studies have shown that the relationship between DNA methylation and histone modifications is mediated by a group of proteins whose function is the binding to methyl groups from DNA, including proteins which bind to CpG methylated islands (MeCP2), proteins with binding domain to CpG methylated islands (methyl-CpG binding domain protein 1, MBD1), and Kaiso protein-also known as ZBTB 33 (Zinc finger and BTB domain containing protein 33). These proteins are localized to the methylated promoters and recruit a protein complex containing HDACs and HMTs [105–107]. These studies suggest that DNA methylation may induce structural changes to the chromatin by altering the histone modifications. It is also known that DNA methylation inhibits methylation of histone H3K4me [108, 109]. In embryonic stem cells gene, Oct3/4 is inactivated after the fate is determined to a particular cell type. The silencing process is realized by recruiting a co-repressor complex consisting of G9a methyltransferase and with HDAC enzyme activity. DNMT3A and DNMT3B DNA methyltransferases are subsequently recruited, catalysing the *de novo* DNA methylation at the gene promoter level [110]. Interaction between G9a protein and DNA methyltransferases (DNMT3A and DNMT3B) depends on the ankyrin motif of G9a protein [111]. In exchange, the SET domain responsible for methyl transferase activity of the G9a protein does not interact with DNA methyltransferases [112, 113]. These data suggest that DNA methylation at the promoter level depends on recruiting especially G9a protein and less of its methyltransferase activity. Interaction between histone H3K9 methylation and DNA methylation represents a model in which these two changes determine a strong silencing loop or bidirectional interference.

Recently, it was established with the aid ChIP and bioinformatics a link between methylation-mediated by PCG on histone H3K27 and *de novo* DNA methylation in cancers, which claims that the signal required by PRC2 during development predisposing certain genes to *de novo* methylation later [113–115]. In tumor cells were observed interactions between DNA methyl-

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ation and histone H3K9 methylated, thereby contributing to a stable silencing mechanism. PCG and EZH2 proteins are members of Polycomb repressor complex 2 (PRC2) which has methyltransferase activity with substrate specificity for histone H3K27. Histone H3K27me3 serves as specific binding signal to a chromodomain of another Polycomb repressor complex (PRC1). PRC1 blocks transcriptional factors recruitment, therefore the presence of PRC1 stops transcription initiation.

Biochemical studies have also shown that DNA methyltransferase binds EZH2 to certain conditions [115–117]. Histone H3K9 and H3K27 methylation presence does not always lead to the *de novo* DNA methylation. A subset of target genes for complex PCG can be methylated in cancer. Additional factors are required for DNA methylation in genes showing changes in the histones. Recently, it has been shown that the histone H3K27 trimethylation is PCG mediated and is a mechanism that determines tumor suppressor gene silencing in cancer, which is independent of promoter methylation [118, 119]. This lack of dependence between DNA methylation and histone modifications of these studies demonstrated conflicting results of previous studies. It should be noted that most of the genes presenting at their level histone H3K27me3 in prostate cancer do not show islands CpG motifs in the promoter, instead gene targeted by PCG complexes show generally the CpG promoters islands in embryonic stem cells ES [120]. This indicates that the histone H3K27 methylation processes mediated by the PCG complex in ES, normal and tumor cells are different because the tumor cells by removing the functional path of histone H3K27me3 usurps silencing mechanisms. Therefore, it was established the existence of 3 directions involved in silencing machinery associated H3K27 methylated histone mediated by PCG complex. The first relates to *de novo* repressed genes by methylation of histone H3K27, PCG mediated, and targets certain gene in particular which do not present CpG islands at promoter level. The second direction supports that during oncogenesis an early gene subset became methylated and CpG islands of the promoters are initially marked by PCG complex. This includes also those genes which undergo epigenetic reprogramming and are silent initially by the PCG and then suffer DNA methylation process like an alternated silencing mechanism. This epigenetic silencing switch through DNA methylation reduces epigenetic plasticity, blocking key regulators and contributes to tumourigenesis [121]. Third mechanism supports the fact that DNA methylation and histone H3K27me3 coexist at the same promoter and methylation H3K27me3 histone by PCG silencing machinery is dominant. The silencing machinery may contribute to oncogenesis process in various forms, which can constitute in a repressor mechanism from flexible to plastic up to stable inactivation maintained by DNA methylation.

3.8. Chromatin and cancer

The involvement of DNA methylation process and chromatin changes in oncogenesis is indisputable, but separation of the genetic from epigenetic events is artificial. New evidence has shown that primary genetic defects (mutations in the genes coding for the receptors of growth factors, adhesion molecules, the gene that affects the DNA methylation and histone modifications as DNMT, HAT, or HDAC) lead to altered DNA methylation and changes in chromatin pattern. Both the endogenous and exogenous carcinogens do not cause genetic

mutations but first epigenetic alterations, which highlights that epigenetic alteration is a step in oncogenesis.

All classical genetic alterations as mutations in tumor suppressor genes and in oncogenes can affect gene transcription (e.g., mutations in Ras gene, HER2 gene amplification). It is not surprising that the control of gene transcription machinery can be directly involved in oncogenesis. Although the complex nature of transcriptional regulation is uncertain, balance disruption of enzymatic activity responsible for maintaining acetylated histones status is expected to occur in cancer. p300/CBP histone acethyltransferase gene exhibits mutations in various cancer type (lung tumors, esophageal, ovarian, and gastric) [122–125]. Chromosomal translocations that targeted CBP/p300 gene locus affects transcription by their merger the translocated fragment with genes located in the chromatid area where they were joined (event met in hematological cancers such as acute myeloid leukemia) [126, 127].

Limited data regarding the global profile of histone modifications in oncogenesis can be found, but as a highlight is the overall loss of H4K16 monoacetylation and H4K20 trimethylation [128]. It has also been found that an important role in tumourigenesis is represented by changes of histone from promoters of tumor suppressor genes that determine their silencing. Such modifications are the loss of histone H3K9 acetylation and di/trimethylation of H3K4, H3K9 dimethylation, or trimethylation of H3K27 [129]. Several studies have reported a high level of EZH2 expression, which promotes tumor growth in both *in vitro* and *in vivo*, as identified in a number of human cancers such as melanoma, leukemia, prostate, and breast cancer [130, 131]. It has been shown that EZH2 could be a potential biomarker, and its expression was correlated with aberrant H3K27 trimethylation and silencing of tumor-suppressor genes [119, 132].

Another frequent mechanism in cancer is the inactivation H3K27 demethylase-UTX/KDM6A (lysine *(K)-specific demethylase 6A*). KDM6A gene mutations have been reported in many types of tumors: multiple myeloma, esophageal squamous cell carcinoma, and renal cell carcinoma [133].

3.9. Alteration of histones changes in cervical cancer

Histone modifications and alterations have recently begun to be studied in the cervical cancer. Analysis of histone modifications in the progression of cervical lesions is relatively at the beginning, there are few studies which indicate an association between alterations of histones and cervical cancer development. There are some data supporting that chromatin pattern in cervical samples may help in cervical neoplasia diagnosis, particularly for glandular lesions. The molecular basis of chromatin modifications is not fully determined [134]. E6 and E7 viral oncogenes expression is essential but not sufficient for neoplastic transformation, many studies highlight the important role of epigenetic changes in cervical carcinogenesis. Recently, it has been shown that E6 and E7 oncoproteins interacts with histone-modulating enzyme, which regulates transcription via the host cell chromatin [84]. A recent report showed that in tumourigenesis, tumor cells lose monoacethylated and trimethylated histone H4 (acetylated Lys16 and trimethylated Lys20) form, that being associated with hypomethylation of repetitive

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DNA sequences [135]. Huang et al. [136] showed that the expression levels of HDACs were found to be increased in cervical dysplasia and invasive carcinoma.

It was reported that MGMT a DNA repair protein silencing seems to be associated with a reduction in acetylated histones [137]. Moreover, the activation of Wnt signaling pathway may be realized by a transcriptionally repressed Wnt antagonist DICKKOPF-1 (DKK-1), by histone deacetylation in HPV-infected cervical cells [138]. HDAC function is necessary for HIF-1 (hypoxia inducible factor-1) activity, and it was found that E7HPV protein can block the interaction of HDACs with HIF-1α, activating HIF-1-dependent transcription for a range of pro-angiogenic factors [139, 140]. Silencing of proliferation repressor protein osteo-protegerin (OPG) and retinoic acid receptor β2 (RAR-β2) was found to occur through histone modification as well as DNA methylation [141, 142].

It has been shown that phosphorylated and acetylated forms of histone H3 in cervical swabs are associated with progression from CIN I to CIN II and CIN III [143]. The balance between HDACs and HATs activity has a key role in regulating gene transcription [144]. This balance must be maintained in normal cells, to prevent an uncontrolled proliferation and cell death. E6 and E7 HPV target numerous cellular proteins to disrupt cell growth and proliferation, including HDACs and HATs. E7 hr-HPV protein binds to HDACs, this interaction being performed by Mi2β, a member of the nucleosomes remodeling complex and acetylation of histones (NuRD), which possess the ability to modify chromatin structure by both the deacetylation of histones and by the repositioning ATP-dependent nucleosomes [145]. The interaction the E7-HDACs is independent of binding to Rb protein and E7 gene mutations abolish its ability to target the HDACs and to transform mouse fibroblasts [84]. E6 hr-HPV protein shares with other DNA tumorigenic viruses' ability to target CBP/p300. The interaction involves C-terminus zinc finger of E6 protein and 1808–1826 residues of CBP; as a result, the p53 transcriptional activity is reduced, independently of p53 protein removal through the proteasome degradation pathway [146]. E7, E6 protein binds to the transcriptional co-activator p300/CBP, being a crucial step in cellular transformation [147].

Histone methylation is acknowledged to be a dynamically process controlled by two types of enzymes that work together to maintain global histone methylation patterns: HMTs and histone lysine demethylases (KDMs) [42, 95]. Histone methylation can occur at different lysine residues. The interaction between HMTs and KDMs locally adjusts the degree of methylation which results in the activation or repression of gene expression, depending on the specific target lysine residue [95]. Thus, the degree of methylation and the position of methylated lysine have different consequences: overall methylation of H3K9 (histone 3 lysine at position 9), H3K27 (histone 3 lysine at position 27), and H4K20 (histone 4 lysine at position 20) is linked to the heterochromatin formation in the presence of a transcriptional repressor associated with HP1, while the methylation of H3K4 (histone 3 lysine in position 4) and H3K36 (histone 3 lysine in position 4) is associated with transcriptionally active regions [148–152]. Generally, methylated H3K4, H3K36, and H3K79 are considered activating marks, whereas methylation of H3K9, H3K27, and H4K20 are often associated with gene silencing [150–154].

E6, E7 oncoproteins can associate with enzymes that modulate histone acetylation, and thus, regulate the transcriptional capacity of host cell chromatin [151, 152, 155, 156]. Especially,

KDMs expression was found to be deregulated and associated with cancer aggressiveness. KDMs were further proposed as potential tumor biomarkers and could play distinct role in cancer progression acting either as putative oncogene or tumor suppressor based on different transcriptional role (gene activation/repression) [157, 158].

McLaughlin-Drubin *et al*. [159] sustain that E7 HPV16 can induce epigenetic and transcriptional alterations by transcriptional induction of the KDM6A and KDM6B histone 3 lysine 27 (H3K27)-specific demethylases.

KDM5C demethylase role in the pathogenesis of HPV-induced has been described in the literature. KDM5C is recruited by the E2 viral protein for E6 and E7 oncogenes transcriptional repression through the LCR region of HPV. The results obtained indicate KDM5C as a good marker for severe lesions and SCC [160].

Another recent study showed that KDM4C, KDM5C, KDM6A, and KDM6B genes expression significantly increase in high-grade lesions (CIN 2+) and SCC presenting a positive correlation with HPV infection. A significantly increased of KDM4C expression levels in SCC samples compared with precancerous lesions propose it as a suitable tumor marker. KDM4C/GASC1/JMJD2C/ is a histone demethylase that is mainly regarded as oncogene due to its role in demethylating heterochromatic H3K9me3/2 [161]. Another good marker for high-risk lesions and SCC seems to be KDM5C whose expression levels were found increased in CIN2+ lesions and significantly increased in SCC cases [160, 161].

p16 gene expression in normal cells is generally low due to gene silencing by H3K27 trimethylation and PRC complex action. It was observed that the E7 oncogene expression may reduce residues H3K27 required for repression of PRC1 complex, leading to transcriptional activation of histone H3K27, histone demethylases KDM6A, and KDM6B through an unknown mechanism. In response to the stimulation of the RAS/RAF transcriptional activation of KDM6B occurs possible via AP1, leading to the removal of H3K27me3 (histone 3 lysine at position 27 trimethylated) residues and increasing expression of p16INK4a [162]

The literature data suggest an important role as biomarker for p16INK4a tumor-suppressor gene in HPV-induced lesions and cervical cancers. The mechanism of induction of p16 expression by the E7 viral oncogene is believed to be achieved by the activation of E2F transcription factor [163]. Later it was observed that from the p16 promoter are missing response elements to E2F and E7 HPV16 mutated variants that are defective in binding/degradation of pRb and E2F transcription are not activated; p16 expression can be induced by the wild-type and variants [159]. p16INK4 expression is induced by demethylation of H3K27 residues KDM6B mediated, that underpins the induction of senescence by oncogenes (*Oncogene induced senescence*—OIS), an intrinsic cellular innate tumor suppressor mechanism triggered by oncogenes such as RAS [164]. E7 oncogene causes degradation of pRB, the main mediator of halting cell growth and senescence induced by p16, repealing the mechanism of induction of senescence by oncogenes. The mechanism of inactivation of pRB by E7 can be explained by the necessity to avoid eliminating E7 HPV positive cells targeted by OIS. Such high levels of p16 observed in this study correlated with an increased expression of KDM6B histone demethylase due to E7 oncogene activity on H3K27 modulators.

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4. The impact of HPV infection on ncRNA in cervix oncogenesis

In the latest years, thanks to a growing number of studies focusing on high-throughput next generation sequencing (NGS), large-scale genome, and genome-wide transcriptome methods, a new world of RNA molecules: ncRNAs have emerged [165].

More recently, through deep sequencing data obtained by transcriptome projects such as ENCODE (Encyclopedia of DNA Elements Consortium), it has been revealed that around 90% of genomic DNA in eukaryotes is transcribed with just 1–2% of the transcript encoding for proteins, the vast majority being transcribed as ncRNAs [166].

Some of the ncRNAs molecules appear to be important players in genome functioning acting as "regulatory RNAs". Experimentally data gathered so far sustain the ncRNAs involvement in many biological processes; they seem to have important roles in genes transcriptional and posttranscriptional regulation, RNA splicing, translation and turnover, also in epigenetic modifications [167, 168].

Furthermore, given the regulatory role that these non-coding molecules possess in normal biological processes, it has been presumed that they might play a significant role also in different types of pathologies. There are accumulating evidence highlighting a major role for these molecules in various diseases where they appear to have aberrant expression and contributes to disease development and progression.

Several studies showed ncRNAs involvement in diseases such as neurodegenerative, cardiovascular, immune diseases and in neoplastic transformation [169]. Regulatory ncRNAs could be classified according to their length in three categories [170]:

- Small ncRNAs (approximately 18–31 nucleotides) which comprises: small interfering RNAs (siRNAs), microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs).
- Medium ncRNAs (31–200 nucleotides): promoter-associated small RNAs (PASRs), terminal-associated small RNAs (TASRs), transcription initiation (tiRNAs).
- Long ncRNAs (lncRNAs) (>200 nucleotides in length) that includes: long intergenic ncRNAs (lincRNAs), pseudogenes, sense and antisense RNA, enhancer RNAs (eRNAs).

miRNAs molecules are approximately 18–24 nucleotides in length, ncRNAs that regulate genes expression in eukaryotic organisms. These RNA molecules are known to be a part of RISC complex (RNA-induced silencing complex) and are involved in gene silencing by pairing with complementary sequences at 3' UTR (untranslated regions) or coding region of a target messenger RNAs (mRNAs) that leads to mRNA degradation and blocking protein synthesis [171–173].

Through this interaction miRNAs molecules play an important role in specific cellular processes including cellular development, proliferation, differentiation, apoptosis, and thereby controlling the expression level of hundreds important genes involved in these processes [174, 175].

Numerous studies have reported miRNAs aberrant expression profiles in different types of cancer. Until recently, the most extensively studied ncRNAs in oncogenesis, miRNAs appear to have a dual nature in neoplastic transformation acting either as tumor suppressors and/or as oncogenes depending on the cellular context [176].

miRNAs known to have oncogenic functions also called "oncomiRs" have frequently been demonstrated to control processes such as cell differentiation, apoptosis, and tumor development through tumor suppressor genes inhibition. Several examples of well-known oncomiRs linked to malignant transformation are miR-15, miR-16 found upregulated in many types of leukemia's and lymphomas [177, 178]; miR-155 overexpressed in chronic lymphocytic leukemia (CLL), B-cell lymphoma, anaplastic large cell lymphoma (ALCL), Hodgkin's or Burkitt's lymphoma and in breast tumors [179–182]; miRNA-17-92 cluster (oncomiR-1) deregulated in multiple types of cancer: lung (particularly in small-cell lung cancer and aggressive forms), pancreatic, hepatocellular, colorectal, breast, ovarian, and hematopoietic cancers [183, 184]; meanwhile, miR-106a has an oncogenic role in pancreatic, colon cancer, and T-cell lymphoma [185–187]; another promising oncomiR is miR-21 found overexpressed in various cancers including breast cancer, lung cancer, colorectal cancer, hepatocellular carcinoma, glioblastoma [188–196].

On the other hand, in cancer, it was shown that some miRNAs are consistently downregulated and act as tumor suppressor with example such as: miR-15a and miR-16 cluster that is often deleted or downregulated in tumor cells [197–200] or miR-34 family members that were identified as potential tumor suppressor in many cancers [201–203], also miR-124 was found significantly downregulated in several types of human cancers [203–206]; miR-122 demonstrated to regulate intrahepatic metastasis in hepatocellular carcinoma and thus acting as a tumor suppressor for this pathology [207] and mir-203 was shown to suppress cell proliferation and migration in various types of cancer [208–210].

A malignancy where miRNAs role has been extensively investigated is cervical cancer. There are many reports that emphasize a substantial role for these non-coding molecules in cervical oncogenesis.

An interesting research direction in miRNAs field is their relationships with viral infections. Various studies support the fact that some cellular miRNAs expression can be regulated by virus infection and these observations are not surprising given the host defense mechanisms against pathogen agents such as bacteria and viruses.

Researchers also have identified several cellular miRNAs whose levels can be modulated by HPV infection, respectively, by viral E6 or E7 oncoprotein of high-risk genotypes [211].

Studies based on miRNAs expression profiles revealed a differentially pattern of expression in cervical tumors tissue compared with normal tissue, still due to different detection methods and experimental systems use in some cases the observations are contradictory (**Table 2**).

Recently based on the observation that some viruses could express their own set of miRNAs, there is an ongoing effort to identifying these miRNAs and to establish their role during viral infection. Reports revealed that miRNAs encoded by viruses target host genes involved cell

miRNA	Expression pattern	miRNA detection method	References
-21	High	Microarray, Northern blot, qRT-PCR	[212–214]
-27a	High	qRT-PCR	[214]
-34a	High	qRT-PCR	[214, 215]
-155	High	Microarray, Northern blot, qRT-PCR	[214, 216, 217]
-146a	High	Microarray, Northern blot	[216]
-125	High	qRT-PCR	[215]
-196a	High	qRT-PCR	[214, 218, 219]
-203	High	qRT-PCR	[214, 220, 221]
-138	High	qRT-PCR	[222]
-7	High	qRT-PCR	[221]
-20a	High	qRT-PCR	[220, 223]
-221	High	qRT-PCR	[214, 224]
-200	High	qRT-PCR	[225]
-93	High	qRT-PCR	[225]
-124	Low	qRT-PCR	[226, 227]
-143	Low	Microarray, Northern blot, qRT-PCR	[216, 228]
-145	Low	Microarray, Northern blot	[216, 229]
-149	Low		[212]
-195	Low	Microarray	[230]
-34a	Low	qRT-PCR, Northern blot	[231, 232]
-214	Low	Northern blot, qRT-PCR	[233]
-23b	Low	Microarray	
qRT-PCR	[212, 234]		
-519	Low	Northern blot, qRT-PCR	[235]
-218	Low	Northern blot, qRT-PCR	[236]
-372	Low	qRT-PCR	[237]

Table 2. Examples of miRNAs aberrant expressed in cervical cancer.

proliferation, apoptosis, host immunity regulation, in order to maintain their survival and to escape from immune system response.

Over 200 miRNAs encoded by several virus families have been identified to date, many of them being found for herpes viruses and Epstein–Barr virus (EBV) [237]. For instance, it was found that EBV encodes more than 40 miRNAs that presents different expression levels during viral infection and some are involved in maintaining viral latency [238, 239]. From our knowledge to date, there are no reports on the existence of HPV-encoded microRNAs.

Although researcher's attention in latest years was mainly focus on short ncRNAs molecules and their functions in normal/pathological conditions, at present great efforts are put into investigating the major part of the non-coding transcriptome namely lncRNAs transcripts.

It has been revealed that certain lncRNAs can control gene expression through a range of different mechanism including transcriptional, splicing, and post-transcriptional regulation or at epigenetic levels by chromatin remodeling and histone modification regulation [240–242].

Even though few lncRNAs have been well characterized, from the knowledge accumulated so far it is clear that they represent significant gene regulators and play critical roles in many

cellular and development processes. Therefore, taken into account, the wide functions that lncRNAs hold, it is not surprising that their alterations are associated with an extensive range of disease.

Several studies have reported lncRNAs involvement in cardiovascular diseases, neurological disorders, immune disease, and also in cancer, data indicates a differential lncRNAs expression in many types of malignancy including, breast cancer, colon cancer, prostate cancer, hepatocellular carcinoma, pancreatic cancer, lymphomas [243].

Currently, the expression profile of various ncRNAs has become an important feature of oncogenesis process. There are numerous publications indicating an association between lncRNAs expression and malignant transformation and the number is still rising. Despite the keen interest shown by these molecules for many of them, the functional role in normal/pathological condition is still unclear, additional studies are needed. Recently with the help of the latest NGS techniques, new information is brought to light for better understanding lncRNAs role, mechanisms of action, and also the potential use of them in various cancer therapies.

Among the best well-characterized lncRNAs are XIST (*X inactive specific transcript*) a 17-kb-long transcript known for its role in dosage compensation involving X chromosome inactivation and H19 transcript 2.5-kb-long that plays an important role in imprinting [244, 245].

Experimentally data sustain a potential oncogenic role for H19, an aberrant expression have been identified in a variety of cancers: breast, ovarian, hepatocellular, gastric, lung, colon, esophagus [246–251]. It has been shown that H19 oncogenic role is also due to the fact that the transcript acts as a precursor for miARN-675 leading to pRB gene expression decrease [252].

Another lncRNA having oncogenic potential is MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) who it was suggested in many studies that can promote cell proliferation apoptosis, invasion, and metastasis. Significantly high levels of MALAT1 expression were detected in lung cancer, prostate cancer, colorectal cancer, hepatocellular carcinomas, gynecologic (endometrial, cervical) cancer, osteosarcoma [253–262].

There are identified lncRNAs that appear to have tumor suppressor function in carcinogenesis. For GAS5 (growth arrest specific 5) lncRNA, it was found to play an important role in apoptosis induction; studies have reported a significantly reduced GAS5 levels of expression in breast cancer and prostate cancer [263, 264]. Another report shows that GAS5 low level of expression is associated with poor prognosis in hepatocellular carcinoma [265].

MEG3 (maternally expressed 3) is lncRNAs that presents a reduced expression in several types of cancer. Several experimental evidences demonstrate that MEG3 interacts with p53 tumor suppressor gene and regulates p53 target gene expression, therefore, inhibits tumor cell proliferation and cancer progression. Aberrant levels of MEG3 expression have been identified in glioblastoma, ovarian, colon, cervical, lung cancer [266–271].

In literature, there are a relatively small number of experimental data showing an association regarding lncRNAs involvement in cervical carcinogenesis, but due to high interest shown

toward these molecules the number is growing fast. The data collected so far on lncRNAs involvement in cervical cancer are presented in **Table 3**.

LncRNA name	Functions	Expression pattern	References
H19 (imprinted maternally expressed transcript)	Located in an imprinted region near the insulin-like growth factor 2 (IGF2) gene. Potential dual role in oncogenesis (tumor suppressor/oncogene)	Upregulated	[275]
HOTAIR (HOX antisense intergenic RNA)	Located within the Homeobox C (HOXC) gene locus is co-expressed with HOXC genes. Involved in HOXD genes transcription repression via histones methylation using PCR2 and LSD1 complex	Upregulated	[276–279]
XIST (X inactive specific transcript)	Role in X chromosome inactivation	Upregulated	[280]
MALAT1 (metastasis-associated lung adenocarcinoma transcript 1)	Regulates transcription of genes involved in cancer metastasis cell migration, proliferation and cell cycle regulation	Upregulated	[281, 282]
ANRIL/CDKN2B-AS1 (Antisense non-coding RNA in the INK4 Locus; CDKN2B antisense RNA 1)	Located within the CDKN2B-CDKN2A gene cluster; interacts with PRC1 and PRC2 complexes for epigenetic silencing of genes in this cluster	Upregulated	[283, 284]
TUSC8 (tumour suppressor candidate 8; XLOC_010588)	Unknown	Downregulated	[285]
BC200/BCYRN1 (brain cytoplasmic RNA 1)	Encodes a neural small non-messenger RNA	Upregulated	[286]
lncRNA-EBIC (TMPOP2—thymopoietin pseudogene 2)	Unknown	Upregulated	[287]
GAS5 (growth arrest specific 5)	Promotes cellular growth arrest and apoptosis	Downregulated	[288]
MEG3 (maternally expressed gene 3)	Inhibits tumor cell proliferation; a potential tumor suppressor role due to p53 activation	Downregulated	[269]
lincRNA-p21 (TP53COR1—tumor protein p53 pathway corepressor 1)	Repress genes transcriptionally regulated by p53	Upregulated	[283]
lncRNA-LET (NPTN-IT1—NPTN intronic transcript 1)	Stabilizes nuclear factor 90 protein, promotes hypoxia	Downregulated	[289]
CCHE1 (CCEPR—cervical carcinoma expressed PCNA regulatory lncRNA) *CCND1 ncRNA* (cyclin D1 non-coding RNA)	Regulates cyclin D1 gene expression	Upregulated Upregulated	[290] [283]
SncmtRNA (Sense mitochondrial ncRNA) *ASncmtRNA* (Antisense mitochondrial ncRNA transcript)	Unknown	ASncmtRNA Downregulated SncmtRNA-2 (Upregulated)	[291]

Table 3. List of lncRNAs expressed in cervical cancer [272–274].

5. Epigenetic changes involved in viral gene expression

Methylation status of integrated HPV depends of viral life cycle as well as of neoplastic transformation, this making HPV methylome a potential tool in cancer diagnostic. HPV genome methylation status depends on the viral life cycle and is associated with neoplastic progression.

According to Johanssen and Lambert study, viral genome is subjected to *de novo* methylation by host DNMTs. Methylation of the viral genome may be a part of a mechanism involved in innate response to pathogens by which the host attempts to suppress viral gene expression.

The authors note that in HeLa cells, HPV18 genome chromatin histone modification status correlates with the occupancy of host transcriptional machinery specifically within the LCR [292]. E7 and E6 oncoproteins of hr-HPVs appear to modulate host epigenetic machinery through their interplay with both DNA methylation enzymes as well as chromatin remodeling enzymes [159].

Mirabello et al. [293] reported in 2013 that they found 3-region in L1 strongly methylated in cancers and only in a small percentage in CIN I and CIN II lesions. In addition, the authors shown that methylation at certain CpG sites can indicate an evolution toward CIN II+ years before it happens.

Evaluation of cervical samples from HPV positive women, presenting precancerous lesions or invasive ones, showing that the hypomethylation degree in LCR and E6 gene region increase with the increasing of lesion severity. These data convinced the authors to conclude that neoplastic transformation could be suppressed by hypermethylation, while hypomethylation accompanies or leads to progression toward cancer [294].

Using laser microdissection on different layers from samples with HPV-infected lesions, Vinokurova and von Knebel Doeberitz [295] found dynamic changes in HPV16 LCR methylation in the context of the viral life cycle. A decrease in methylation in the transcriptional enhancer region within the LCR was observed in terminally differentiated epithelial compartment and meanwhile an increase in methylation within the region of the LCR containing the early promoter was noted [295].

Another study highlighted heterogeneity of methylation status among patients, even in samples from the same patient. Methylation frequency was found to be approximately 30% in L1 region, less than in CpG islands around enhancer and promoter of HPV16. In most of the HPV genome sites, hypermethylation is associated better with carcinoma than with dysplastic lesions [296].

On the other hand, a study regarding methylation status in HPV18 immortalized cell lines (HeLa and C4-1) and in samples from patients, determined a clonally heterogeneity of methylation status in different regions of viral genome. The clinical samples showed partial or total methylation in HPV enhancer region, while in asymptomatic patient's, samples were fully unmethylated. Viral promoter was reported to be methylated in tumor samples and in cervical smears [297].

These studies indicate that methylation status of viral oncogenes in cervical lesions could be the result of transcriptional activity level and not an event that leads toward neoplastic progression. Further studies regarding the influence of DNA methylation on viral life cycle focused on E2 (early gene involved in viral transcription and replication) gene methylation. *In vitro* studies revealed that HPV16 URR (upstream regulatory region) methylation inhibit E2 protein capacity to bind DNA [298]. By looking at methylation status of E2BS (E2 binding sites) in immortalized epithelial cells from a HPV16 positive patient, Kim *et al*. found this region to be selectively hypomethylated in highly differentiated cell population, while heavily methylated in basal-like differentiated cells. The conclusion was that methylation status of E2BS may vary during the viral life cycle, this giving an insight on E2 modulation function during

progression of infection [298]. E2BS is more frequently found in a hypermethylated state in cervical lesions with extrachromosomal state of viral genome, while upon integration in the host genome, it was found to be hypomethylated, except the cases in which viral genome integrates as a concatemer, when only a small proportion are found hypomethylated and most of them hypermethylated [292].

All this experimentally observations conclude that HPV genome methylation status could hold a prognostic and progression value for cervical lesions.

6. Potential epigenetic biomarkers in cervical cancer

Cancer epigenome is currently in the researchers spotlight due to the fact that all the epigenetic changes that accompany cervical carcinogenesis can be exploited as biomarkers. Thus, once deciphered, the epigenetic peculiarities of cervical cancer might be used in the development of new alternatives for screening or for the assessment of prognostic [299]. On the other hand, the reversible nature of epigenetic alterations makes them attractive targets for new therapeutic approaches. Some of these discoveries have been proposed as investigation methods or resulted in new treatment approaches and commercial tests [300]. By far, the most studied epigenetic changes are the methylation patterns, especially the methylation markers of the host. Abnormal methylation of promoters of tumor suppressor genes is common in different type of cancers with the prospect of becoming a biomarker in oncology [301]. As the methylation profile of these genes increases with the severity of cervical lesions, their status might be used as potential biomarker for early detection of cervical cancer disease [302]. For a better stratification of cervical cancer and precursor lesions, different specific methylation panels have been suggested [303]. Using DMH (differential methylation hybridization) technique and qPCR, Lai et al. [304] found in scrapings isolated from CIN3 lesions, a higher frequency of methylation for SOX1, NKX6-1, PAX1, WT1, and LMX1A genes. Siegel et al. [305] demonstrated that aberrant methylation levels of DAPK1, RARB, WIF1, and SLIT2 might increase specificity to identify cervical cancer compared to viral testing alone. Also, the methylation patterns of GGTLA4 (183 bp) and ZNF516 (241 bp) genes were proposed in a patent as biomarkers for diagnosis of premalignant cervical lesions [306], while aberrant methylation of PAX1, PTPRR, SOX1, and ZNF582 promoters were suggested as markers for AC screening [307]. The studies that associate the methylation profile with cervical lesion severity have resulted in a commercial test (GynTect) [308]. GynTect assay is based on methylation-specific PCR (MS-PCR) and, if positive, detects specific methylated DNA sites in cervical smears. Manufacturer recommend the test for cervical cancer screening, allowing the triage of women over 30 years who tested positive for HPV. Moreover, GynTect may be performed using residual material from the HPV test. So, this methylation assays might be use as a secondary marker after HPV DNA testing in order to guide the subsequent clinical approach (referral to colposcopy or initiating a certain therapy) [309].

Other authors correlated changes in host DNA methylation with the development of drug resistance. Chen et al. [310] identified both genome-wide and within individual loci changes in an oxaliplatin-resistant cervical cancer cell line derived from SiHa cell line. The methylation of *Casp8AP2* gene resulted in increased drug resistance in different cells.

Masuda et al. [311] reported that aberrant methylation of Werner (WRN) gene that encode for a DNA helicase, increased the sensitivity to CPT-11 (an inhibitor of DNA topoisomerase I). Iida et al. [312] reported aberrant hypermethylation of CHFR (checkpoint with forkhead and ring finger) in adenocarcinoma and HeLa cell line (immortalized with HPV18) and correlated this profile with lower sensitivity to anticancer therapy when compared to SSC, proposing this pattern in adenocarcinoma as a potential biomarker for sensitivity to paclitaxel. Therefore, the identification of methylation patterns associated with drug-resistance might become a valuable tool in cervical treatment with demethylation agents that can revert this epigenetic change.

Regarding the methylation of viral DNA, data are still under debate. While some authors have suggested that it is a defense mechanism of the host cell, others considered it is a way by which the virus contributes to persistent infection. [313]. Other researchers considered that neoplastic transformation may be suppressed by HPV CpG methylation, while demethylation occurs as the cause of or concomitant with neoplastic progression [314]. Several authors proposed HPV16 L1 ORF methylation as a predictive marker for CIN3+ [315] and elevated levels of CpG 6367 L1HPV16 methylation as marker to predict future CIN2+ in women older than 28 years [293]. Also, Mirabello et al. [316] correlated elevated levels of CpG methylation in the L1, L2, E2/E4 with CIN3 or worse and data were confirmed by other papers [317]. Moreover, Wentzensen et al. [317] found differential methylation patterns in CIN3 patients with multiple infections thus suggesting a possible way to identify the causal type of HPV.

Cervical carcinogenesis is accompanied also by altered expression of methyltransferases. For therapeutic purpose, Hamamoto et al. [318] had synthesized double-stranded molecules that inhibit the expression of SUV39H2 (suppressor of variegation 3–9 homolog 2) gene. This gene encodes a HMT that methylate the H3K9 lysine residue and its hyperexpression correlates with carcinogenesis. The silencing of CHFR through its promoter hypermethylation leads also to the activation of DNA methyltransferases (including DNMT1). Different patterns of demethylation obtained by silencing DNMT1 in experimental model (HeLa and SiHa cell lines) indicate the inhibition of DNMT1 as a target for the treatment of cervical cancer with HPV18 infection [312]. These results showed that infection with different HPV genotypes differently interfere with epigenetic mechanisms.

Molecular investigations of cervical tumors and cell lines immortalized with HPV have shown that, from all ncRNA molecules, miRNAs profile is significantly changed when compared to normal tissue, even in early stages of carcinogenesis [309]. Zheng et al. [319] provided data that viral E6 and E7 oncoproteins deregulate the expression of several miRNAs via the E6-p53 and E7-pRb pathways. In turn, miRNAs may influence the expression of HPV genes by targeting viral RNA transcripts, these recommended miRNAs as new biomarkers in cervical screening. The panel of four circulating miRNAs (miR-16-2*, miR-195, miR-2861, miR-49) [320] are suggested as predictive biomarkers for the prognosis of cervical cancer patients, upregulate expression of serum miR-205 [321] and serum pattern of miR-29a and miR-200a may indicate tumor histological grade and progression stage [322]. Li et al. [323] found lower levels of miR-218 levels in patients with high-risk HPV comparing with control or those with low-risk or intermediate-risk HPV. In Chinese population, Zhou et al. [324] reported a good correlation

between a miR-218 polymorphism and its target laminin 5B3 in cervical cancer invasiveness. Epigenetic changes through methylation of miRNAs might correlate with cervical disease. A panel of three miRs (miR-149, miR-203, and miR-375) was found hypermethylated in HPV-positive cell lines [76] and miR-203 and miR-375 hypermethylation correlated with uterine precancerous lesions [325].

miRNAs might be also used for cervical cancer therapy. On animal model, Liu et al. [227] who noticed an inverse correlation between the expression of miR-143 and Bcl2 suggested the possibility of a therapeutic approach by targeting this pathway. Also, miRNAs might modulate the sensitivity to chemotherapy. For example, miR-375 might be a therapeutic target in paclitaxel-resistance of cervical cancer cells [326], while miR-155 and miR-281 increase sensitivity to cisplatin [325]. Therefore, miRNA deregulation may become a target of the investigations for evaluating the effectiveness of treatments in cervical cancer [327].

7. Conclusions

All these data underline the importance of epigenetic modification in tumor development and cervical cancer risk assessment. Epigenetic alterations could be used as biomarkers for the prognosis and evolution of the disease and for therapy response prediction. New techniques in epigenetic investigations may yield better detection systems in order to identify new and sensitive biomarkers that might contribute to improved screening assays, new therapeutic approaches, and prediction biomarkers. The reversible nature of epigenetic alterations provides new opportunities in the development of therapeutic agents targeting epigenetic modification in oncogenesis.

Conflict of interest

The authors declare no conflict of interest.

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