# Long Noncoding RNAs in HPV-Induced Oncogenesis

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**ABSTRACT:** Long noncoding RNAs (lncRNAs) play important roles in a wide range of oncogenic processes, including malignant transformation, epigenetic reprogramming, epithelial-to-mesenchymal transition, and metastasis development. LncRNAs induced by oncogenic viral proteins were shown to play critical roles in tumor initiation and progression. Despite this, little is known about Human papillomavirus (HPV)-induced modulation of host's lncRNAs. In this review, we gathered published information about altered lncRNAs upon HPV status (infection/protein activity), making use of descriptive research works and published gene expression microarray experiments. A diversity of lncRNAs demonstrated to be altered, including metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), H19, and maternally expressed gene 3 (MEG3). Their functions in several cancers were reviewed, indicating that they may represent potential candidates for future research on HPV-induced oncogenesis.

**KEYWORDS:** human papillomavirus, lncRNA, cancer, ncRNA, virus

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## Introduction

Human papillomaviruses (HPVs) are epitheliotropic viruses that belong to the *Papillomaviridae* family and present specificity for different anatomic sites.[1,2] Close to 200 HPV types were described by DNA genome sequencing.[1–3] The great majority is classified into three genera based on the major capsid protein L1 genomic homology[2–5]: alpha-papillomavirus, isolated predominantly from genital lesions;[6,7] beta-papillomavirus that, reinforced by ultraviolet B irradiation, may be involved in the development of nonmelanoma skin cancer (NMSC), which was first observed in patients with Epidermodysplasia verruciformis;[8–10] and gamma-papillomavirus that, with mu and nu genera, is predominantly observed in cutaneous lesions. HPV genera tropism to anatomical sites allows another clinical grouping: alpha viruses associated as "mucosal" or "genital" types and beta and gamma viruses as cutaneous types.[3,4,9]

These viruses can also be classified by their involvement in the genesis of benign or malignant lesions.[3,11,12] Some viral types such as HPV6 and 11 were associated with benign proliferations such as common warts and condyloma, being considered as nononcogenic or low-risk types.[13,14] On the other hand, HPV16, 18, 31, and 33 were classified as oncogenic or high-risk types in consequence of their strong association with premalignant and malignant cervical lesions.[1,3,9,15]

## HPV Biology and Cancer

HPVs have a nonenveloped capsid of 50 nm in diameter that includes a molecule of double-stranded circular DNA with approximately 8 kb in length.[16] HPV genome contains an average of eight open reading frames, divided into three regions.[4] Effector proteins are transcribed from the early region (second region), which constitutes six open reading frames (E1, E2, E4, E5, E6, and E7), encoding proteins mainly involved in DNA replication, gene transcription (*E1* and *E2*), and cellular transformation (E5, E6, and E7);[4] the first region is a long control region that contains the regulatory function of E6 and E7 transcription; and the third is a late region, which is the genomic site of L1 and L2 that transcribes, respectively, the major capsid protein and minor capsid protein, involved in the assembly of viral particles.[4,17]

HPV is responsible for one of the most frequent sexually transmitted infection in both men and women[17,18] and is strongly associated with uterine cervix,[19] vulva,[20] and anal

tumors in women.[17,21,22] In men, HPV infection is associated with penile and anal cancers,[23] while head and neck tumors are well described in both genders.[24,25] The prevalence of viral infection differs among anatomical sites: HPV DNA is highly detected in cervical cancer,[19] close to 50% in vulva[20] and penile tumors,[23] as well as 20% in oropharynx cancers.[17,26]

It is established that for the development of HPV-associated carcinoma, the activities of the high-risk E6 and E7 proteins are necessary.[10,27] The oncogenic protein E6 promotes tumor suppressor p53 protein degradation via the ubiquitin-proteasome pathway,[28] and telomerase activation by the heterodimer HPV E6/E6-associated protein (E6AP), reinforced by degradation of the hTERT repressor NFX1-91[29–32] and E6 binding to hTERT promoter.[33] Other cellular proteins were identified as E6-interacting proteins, such as PDZ family members (e.g. hDIg, hScribble, MUPP1, PTPN13, PATG, and MAG1),[34] which are related to HPV-induced malignancy,[35] and the transcriptional coactivator p300/chitin-binding protein that results in the downregulation of p53 activity.[36] E6 has also been shown to abolish extrinsic apoptotic signaling by directly binding to the tumor necrosis factor receptor 1 (TNFR-1),[37] thus, avoiding its interaction with the TNFR1-associated death domain, which results in the inhibition of TNFR-1 DD-mediated apoptosis.[37] Intrinsic apoptosis can also be blocked by E6-induced degradation of Bak proapoptotic protein.[38]

On the other hand, E7 oncoprotein binds to and induces the degradation of the tumor suppressor retinoblastoma protein (RB)[39] and affects the expression of S-phase genes by directly disrupting pRB/E2F complex.[40,41] E7 promotes cell proliferation by interacting with the retinoblastoma family members p107[42] and p130,[43] cyclin-dependent kinase (CDK) inhibitor proteins p27[44] and p21,[45] and histone deacetylases.[46,47] The function of E7 can be remarkably extended to promote cell survival by upregulating interleukin-6[48] and the antiapoptotic Mcl-1[26] and activating the AKT/PKB pathway.[49,50]

Although HPV protein interaction with the host's proteins has advanced in the past decades, the complete HPV oncogenic mechanisms remain to be fully elucidated. Investigation of HPV-induced modulation of host's lncRNAs emerges as a possibility to provide new advances in this field.

## Long Noncoding RNAs

Recent studies in transcriptome have demonstrated that nearly 80% of human genome produces noncoding RNAs (ncRNAs),[51] indicating that a much larger fraction of the genome may be involved in the post-transcriptional events in gene expression.[52]

Several classes of ncRNAs have been identified, including microRNA, small nucleolar RNAs (snoRNAs), and PIWI-interacting RNAs (piRNAs). In the past few years, an important component of ncRNA class has been studied: the long ncRNAs (lncRNAs) that are defined as RNAs longer than 200 nucleotides.[53] Strong evidences describe that human genome has more than 14000 lncRNA genes units, associated with the regulation of distinct mechanisms and harboring expression patterns depending on the cell type, developmental stage, or disease situation, such as cancer.[54–57]

lncRNAs can regulate several processes in eukaryotic organisms, although most of their functions and biochemical properties are still unknown. They can be classified according to their genomic location and biogenesis: being expressed from intergenic regions (lincRNA) such as lincRNA-p21[58] and Pint lncRNA;[59] from vestigial genes that lost their coding potential (pseudogene-encoded lncRNAs) as BRAFP1,[60] INTS6P1,[61] and HMGA1P6;[62] from the opposite strand of mRNA (antisense lncRNA) as PCNA-AS1[63] and MDC1-AS;[64] or can be generated by the splicing machinery,[54,65,66] constituting long intronic ncRNA as ci-ankrd52.[67]

lncRNAs influence gene expression by several pathways and are often associated with epigenetic regulation by silencing specific genes[68] and acting as chromatin modulators[69,70] and histone modificators.[52,71] lncRNAs can also alter gene expression through alternative splicing,[72] modulating the rates of RNA polymerase II initiation/elongation,[73] and forming paraspeckles structures.[74] In post-transcriptional levels, lncRNA can act in translation[75] and/or stability of target mRNAs[63] and as decoys for microRNAs, altering protein turnover.[66]

Recent findings have revealed changes in expression levels of lncRNAs upon stresses (e.g. diseases), and their implications in pathophysiology are becoming better understood, particularly in cancer.[76]

## Viral Cancers and Long Noncoding RNAs

Virus-induced modulation of lncRNAs is arising as oncogenic mechanisms for tumor development and progression. In fact, specifically in hepatocellular carcinoma (HCC), lncRNA's modulation by viral proteins has been implicated to increase protumorigenic features by influencing pivotal pathways of carcinogenesis.

In HCC, highly upregulated in liver cancer (HULC) lncRNA plays a central role in hepatitis B virus (HBV) X protein (Hbx)-mediated hepatocarcinogenesis. Hbx directly activates HULC gene promoter via binding to the cAMP-responsive element-binding protein.[77] Once activated, HULC downregulates the tumor suppressor p18 expression, which leads to enhanced cell proliferation *in vitro* and *in vivo*.[77] Interestingly, HULC knockdown abolishes the HBx-enhanced cell proliferation through upregulating p18. This demonstrates the essential role of HULC in Hbx-mediated hepatocarcinogenesis.[77]

Hbx expression can also modulate tumor suppressor lncRNAs, such as lncRNA-Dreh. HBx transgenic mice have decreased lncRNA-Dreh expression, which abolishes its function of inhibiting HCC growth and metastasis *in vitro* and *in vivo*.[78] This lncRNA was reported to inhibit tumor metastasis by combining with the intermediate filament protein vimentin, which appears to change the normal

cytoskeleton structure, thereby inhibiting cell migration.[78] In humans, the ortholog lncRNA-Dreh is downregulated in HBV-associated HCC tissues and has a potential to be applied as an independent prognostic factor for patient survival.[78]

Moreover, HBV integration site in human genome is an important feature in HCC. Chimeric Hbx-LINE1 is an lncRNA produced in consequence of HBV integration (viral–human gene fusion), which can be detected in 23.3% of HBV-associated HCC tumors.[79] HBx-LINE1 activates Wnt/β-catenin signaling, promotes cell motility through epithelial-to-mesenchymal transition (EMT), and correlates with poorer patient survival.[79]

These brief examples point out an importance to study virus-induced modulation of host's lncRNAs in virus-related cancers.

## HPV and lncRNA

Although HPV-induced modulation of host's microRNAs has been recently explored demonstrating its increasing importance for HPV oncogenesis (for detailed review refer to Refs.[80–84]), long ncRNAs have not gained much importance yet, despite their oncogenic functions have been shown in other viral cancers.[77,79]

To date, as per the authors' knowledge, only a couple of examples as metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA and mitochondrial lncRNAs have been directly linked to HPV oncogenic protein activity. MALAT1 expression was shown to be directly affected by HPV16 E6/7 activity, altering CaSki cells proliferation,[85] and is upregulated in oral keratinocytes transfected with HPV16 E6 and E6/7.[86] HPV proteins can also induce SncmtRNA-1 and -2 expression and downregulate ASncmtRNA-1 and -2 mitochondrial lncRNAs transcript levels.[87–89] ASncmtRNA-1 and -2 were shown to have a decreased expression in early cervical carcinoma,[90] whereas ASncmtRNA-2 is induced in aging in endothelial cells, where it appears to affect replicative senescence by possibly participating in the cell cycle arrest in G2/M phase.[91] On the other hand, SncmtRNA-1 correlation with cell proliferation suggests a function for this transcript in cell cycle progression.[87,88]

Besides that, a diversity of works have performed gene expression microarray[92,93] to compare transcriptome alteration upon HPV infection and/or activity, providing candidate's list of HPV-modulated lncRNAs. By analyzing these works, it is noticeable that some lncRNAs are differentially expressed according to HPV status, an indication that they may contribute to oncogenesis. Table 1 summarizes what have been published in this field, and the next section shows the evidence of important oncogenic functions of some well-characterized lncRNAs in cancer.

## Cancer-related lncRNAs

**MALAT1.** MALAT1, also known as nuclear-enriched abundant transcript 2, is a highly expressed lncRNA in lung,[94] pancreas,[94] and a diversity of other healthy tissues and is located on chromosome 11q13, being conserved in several species.[94] MALAT1 transcription is initiated from multiple promoters,[94–96] although it is not known which promoter is predominantly used to drive the expression in specific tissues.[97] Its biological function still remains to be clarified but given its interaction with several splicing factors, such as SRSF1 (ASF/SF2), SC35 (SRSF2), and SRSF3,[98–101] and also considering its nuclear localization in SC35 speckles, MALAT1 might be involved in the regulation of alternative splicing.[96]

MALAT1 is overexpressed in numerous cancers and exerts oncogenic functions, which can lead to cell proliferation and cancer progression.[97] The implication of MALAT1 in lung cancer gained much attention after its discovery in non-small cell lung cancer (NSCLC).[94] In lung cancer, it is known that this lncRNA does not affect alternative splicing but regulates the gene expression of metastasis-associated genes (e.g. GPC6, ADAMTS12, MCAM, and PRKCE),[102] and MALAT1 knockdown inhibits EBC-1 tumor metastasis in the lung, elucidating its involvement in the metastatic cascade *in vivo*.[102]

The oncogenic functions of MALAT1 were also demonstrated to be relevant in colorectal cancer.[103] The functional motif fragment at the 3′ end of the lncRNA is involved in the proliferation, migration, and invasion *in vitro*,[103] and MALAT1 promotes migration and invasion through PRKA kinase anchor protein 9 *in vivo*.[104] Its involvement in metastasis is recurrent in a variety of cancers,[97] while it was shown to have a major function in gall bladder cancer cells by activating the ERK/MAPK;[105] in osteosarcoma metastasis by inducing PI3K/Akt pathway;[106] and in esophageal squamous cell carcinoma contributing to the proliferation and metastasis by modifying the ATM-CHK2 pathway.[107]

In cervical cancer, MALAT1 knockdown in CaSki cells affects cell viability, proliferation, and migration,[108] inducing the expression of caspase-3, -8, and Bax, and suppressing the expression of Bcl-2 and Bcl-xL.[108] More interestingly, MALAT1 expression was shown to be downregulated by HPV16 E6/E7 knockdown in CaSki cells[85] and upregulated in oral keratinocytes transfected with HPV16 E6 and E6/7,[86] which suggest that this virus may upregulate MALAT1 expression directly through E6/E7 proteins to promote cell proliferation.[85] Indeed, the increased expression of MALAT1 was observed in different cells containing p53 mutations (C33A, HSG), those containing DNA tumor viruses that sequester p53 (CaSki, SiHa) and p53-negative cells (SAOS), compared to wild-type p53 (OKF6-Tert).[86] BK virus-infected HSG or Vero cells and murine model of polyomavirus-associated SGD have increased expression of MALAT1 compared to control cells and wild-type animals.[86] This information suggests that MALAT1 overexpression may be a common feature of some viruses that share the p53 inactivation/degradation as infection mechanism, as seen in HPV.

**Table 1.** Altered lncRNAs upon HPV status (infection/HPV protein activity).

| lncRNA | CELL TYPE | EXPERIMENT | EXPRESSION ALTERATION (FC) | p-VALUE | REFERENCE |
|---|---|---|---|---|---|
| CDKN2B-AS | Oropharyngeal or oral tumor | HPV Active vs HPV Inactive | 4.5 | $p < 0.02$ | 92 |
| | | HPV Active vs HPV Negative | 4.4 | | |
| EGOT | Oropharyngeal or oral tumor | HPV Active vs HPV Inactive | 4.4 | $p < 0.02$ | 92 |
| | | HPV Active vs HPV Negative | 4.2 | | |
| NCRNA00185 | Oropharyngeal or oral tumor | HPV Active vs HPV Inactive | –2.8 | $p < 0.02$ | 92 |
| | | HPV Active vs HPV Negative | 9.1 | | |
| | | HPV Inactive vs HPV Negative | –3.2 | | |
| PRINS | Oropharyngeal or oral tumor | HPV Active vs HPV Inactive | 6.4 | $p < 0.02$ | 92 |
| | | HPV Active vs HPV Negative | 3.8 | | |
| TTTY14 | Oropharyngeal or oral tumor | HPV Active vs HPV Inactive | 4.1 | $p < 0.02$ | 92 |
| | | HPV Active vs HPV Negative | 2.7 | | |
| TTTY15 | Oropharyngeal or oral tumor | HPV Active vs HPV Inactive | 3.2 | $p < 0.02$ | 92 |
| | | HPV Active vs HPV Negative | 4.2 | | |
| | | HPV Inactive vs HPV Negative | –3.8 | | |
| XIST | Oropharyngeal or oral tumor | HPV Active vs HPV Inactive | 2.1 | $p < 0.02$ | 92 |
| | | HPV Active vs HPV Negative | –12.7 | | |
| | | HPV Inactive vs HPV Negative | 2.2 | | |
| LINC00152 | Oropharyngeal or oral tumor | HPV Active vs HPV Negative | –2 | $p < 0.02$ | 92 |
| MEG3 | HFK | HPV16 E6 transduction | –1.73 | $p < 0.05$ | 93 |
| | | HPV16 E7 transduction | –1.49 | | |
| | | HPV16 E6/E7 transduction | –2.25 | | |
| PCNA-AS | HFK | HPV16 E6 transduction | –1.22 | $p < 0.02$ | 93 |
| | | HPV16 E7 transduction | 1.61 | | |
| | | HPV16 E6/E7 transduction | 1.07 | | |
| H19 | HFK | HPV16 E6 transduction | 1.28 | $p < 0.001$ | 93 |
| | | HPV16E7 transduction | 1.01 | | |
| | | HPV16 E6/E7 transduction | 1.64 | | |
| MALAT1 | CaSki | HPV16 E6/7 knockdown | Downregulated | $p < 0.05$ | 85 |
| SncmtRNA-2 | HFK | E6/7 transduction | Upregulated | $p < 0.05$ | 89 |
| ASncmtRNA-1 | HFK698, HF18 | HPV16/18 E2 knockdown | Downregulated | $p < 0.05$ | 89 |
| ASncmtRNA-2 | HFK698, HF18 | HPV16/18 E2 knockdown | Downregulated | $p < 0.05$ | 89 |

**H19.** H19 was the first discovered lncRNA.[109–111] H19 is a paternally imprinted gene (transcribed from maternal allele), which locates on chromosome 11p15.5[112] near to IGF2 paternally expressed gene.[113] H19/IGF2 locus is also the genetic location of other transcripts, as the tumor growth inhibitor antisense protein HOTS,[114] the miR-675 precursor,[115] and the long intergenic antisense transcript called 91H,[116] conferring enriched complexity to this locus.[117]

H19 is highly expressed during embryonic development, in the extraembryonic tissues (placenta) and in most fetal tissues, while its expression is repressed after birth,[118,119] being detected at basal levels in some adult tissues such as cardiac, skeletal muscles,[109] mammary, and uterus.[120] Besides that, H19 expression is frequently upregulated in cancer cells, such as breast cancer,[121] esophageal cancer,[122] bladder cancer,[123] and cervical cancer,[124] highlighting its involvement in oncogenic processes.

H19 overexpression exerts protumorigenic features through a variety of mechanisms. It acts as competing endogenous RNA (ceRNA/microRNA sponge) for miR-138 and miR-200a.[125] This activity antagonizes these microRNAs' functions and leads to derepression of their endogenous targets vimentin, ZEB1, and ZEB2, promoting epithelial-to-mesenchymal transition in colorectal cancer that culminates in accelerated *in vivo* tumor growth.[125] Similarly, H19 was shown to antagonize let-7 activity, thereby derepressing its target HMGA2 to promote EMT, invasion, and migration in pancreatic ductal adenocarcinoma.[126]

H19 properties as miR675 precursor also exert oncogenic activities. In gastric cancer, H19 was shown to directly

upregulate ISM1 and indirectly suppress CALN1 expression via miR-675, enhancing carcinogenesis and metastasis.[127] H19/miR-675 function in gastric cancer is extended to the suppression of RUNX1, leading to cancer cell proliferation.[128] In colorectal cancer, miR-675 targets the retinoblastoma protein, leading to a direct increase of tumor cell growth.[129]

Besides microRNA regulation (e.g. ceRNA function) and H19/miR-675 mRNA targeting, H19 activity was demonstrated to promote tumor progression of breast cancer cells[130] and, in HCC, H19 ectopic expression enhances the tumorigenic potential of the cells *in vivo*.[131]

If HPV can directly induce H19 expression, it will be an answer for future research, but a plausible candidate mechanism calls attention. It was already shown that c-Myc significantly induces the expression of the H19 in different cell types (e.g. breast epithelial, fibroblast, and glioblastoma) through direct binding to conserved E-boxes near the imprinting control region, which facilitates histone acetylation and transcriptional initiation of the H19 promoter from the maternal allele.[132] At the same time, it is known that HPV16 infection is tightly associated with c-Myc amplification[133] and, more interestingly, HPV18 E7 is able to conjugate to c-Myc, mediating its transcriptional activity.[134] With this information in mind and considering that H19 is upregulated in HPV16 E6 and/or E7-expressing cells, it is possible that HPV can induce H19 long noncoding RNA expression through c-Myc-induced activity.

**MEG3.** Maternally expressed gene 3 (MEG3), long noncoding RNA, is a paternally imprinted gene located on chromosome 14q32. MEG3 gene belongs to the DLK1–MEG3 imprinting locus, which consists of three known protein-coding genes, including DLK1, RTL1, and DIO3, snoRNAs, microRNAs, and at least three lncRNAs.[135]

MEG3 expression is detectable in many normal human tissues, where the brain and pituitary gland have the highest levels.[136] On the other hand, MEG3 expression is lost in a variety of cancer cell lines, including brain,[136–138] cervix, breast, and colon.[136] How MEG3 expression is downregulated in cancer still remains to be fully elucidated; however, a subset of high-grade meningioma tumors present MEG3 DNA allelic loss,[139] and MEG3 loss of expression due to promoter hypermethylation was described in pituitary tumors[140] and multiple myeloma.[141]

MEG3 has tumor suppressor activity by suppressing MDM2 expression, resulting in increased activation of p53 by avoiding MDM2-mediated p53 degradation.[142] As a consequence, active p53 stimulates GDF15 expression in human cancer cells, culminating in a reduced proliferation. However, MEG3 is also capable to inhibit cell proliferation even in the absence of p53.[142] MEG3 and p53 direct interaction was also demonstrated using ectopic expression of MEG3, which resulted in the enhanced activity of p53, inhibiting cell proliferation and promoting cell apoptosis in U251 and U87 MG human glioma cell lines.[138] In NSCLC, induced expression of MEG3 increased apoptosis and reduced cell proliferation by affecting p53 expression.[143] MEG3 antitumor effect was also demonstrated in bladder cancer, where downregulation of this lncRNA inhibited cell apoptosis and increased cell proliferation by activating autophagy.[144]

A possible HPV-modulated MEG3 downregulation would be advantageous for HPV infection and tumorigenesis since HPV16/18 E6 oncoprotein-induced p53 degradation[28] would probably be reinforced by the increased function of MDM2 as a result of loss of MEG3 function, besides all other MEG3 tumor suppressor mechanisms.

**Other lncRNAs.** lncRNA PRINS (Psoriasis Susceptibility-related RNA Gene Induced by Stress) is involved with psoriasis susceptibility due to its higher expression in uninvolved epidermis of patients with psoriasis compared with both psoriatic lesional and healthy epidermis.[145] PRINS expression is increased under stress environment, such as viral infection (herpes simplex virus), ultraviolet B irradiation, and translational inhibition, while it was showed to be regulated by the proliferation and differentiation state of keratinocytes.[145] Although nuclear factor kappa B (NF-κB) is involved in the cellular stress response, PRINS works independently of this pathway[146] and may mediate nucleophosmin response in the skin in stress conditions.[147] PRINS showed to positively regulate G1P3, an interferon-inducible gene with antiapoptotic effects in cancer cells and, at least in patients with psoriasis, it can contribute to a decreased sensitivity to spontaneous keratinocyte apoptosis.[148]

LINC00152 is a lncRNA that is significantly increased in gastric carcinoma compared to normal tissue and correlates with invasion.[149] LINC00152 knockdown inhibits several oncogenic features, such as cell proliferation, colony formation, cell migration, and invasion in gastric cancer and also promotes cell cycle arrest at G1 phase and triggers late apoptosis.[150] In HCC, the plasma levels of LINC00152 significantly predicted the diagnosis of this cancer.[151]

Eosinophil granule ontogeny transcript (EGOT) is a lncRNA expressed from the antisense strand of an intron of the inositol triphosphate receptor type 1 gene.[152] EGOT is expressed in high levels in human bone marrow and in mature eosinophils and is rapidly upregulated in response to interleukin-5 stimulation of CD34 hematopoietic progenitors, regulating the granule protein major basic protein and eosinophil-derived neurotoxin mRNA levels.[153] In breast cancer, the expression of EGOT is lower compared to noncancerous tissues and these low levels correlate with different malignant properties such as larger tumor size, lymph node metastasis, and decreased overall survival, elucidating an independent prognostic predictor for patients with breast cancer.[154]

The antisense PCNA-AS (or PCNA-AS1) lncRNA is expressed from the promoter region located within the first intron of PCNA gene.[155] PCNA-AS is highly expressed in HCC and its induced overexpression promotes tumor growth

*in vitro* and *in vivo* by increasing the proliferative PCNA mRNA stability via RNA hybridization.[63]

The antisense lncRNA CDKN2B-AS, most commonly known as ANRIL (antisense noncoding RNA in the INK4 Locus), is located within CDKN2B-CDKN2A gene cluster at chromosome 9p21.[156] High ANRIL expression is detected in several cancers: in HCC, which is associated with poor prognosis[157] and regulates apoptosis by epigenetically silencing KLF2;[68] in lung cancer, which associates with worse prognosis and its knockdown decreases cell proliferation, migration, and invasion *in vitro*;[158] in gastric cancer, promoting tumor progression by epigenetically silencing miR-99a/miR-449a and controlling mTOR and CDK6/E2F1 pathway targets;[159] in esophageal squamous cell carcinoma, inhibiting p15INK4b through the TGFb1 pathway;[160] and in non–small cell lung cancer, decreasing KLF2 and P21 expression, and therefore, culminating in cell proliferation and apoptosis inhibition.[161] ANRIL correlation with HPV-associated cancers is yet to be investigated; however, ANRIL downregulation in HPV active samples versus inactive/or negative (Table 1) may reflect the CDKN2A/CDKN2B locus hypermethylation detected in some HPV-positive cancers.[162]

The lncRNA XIST gene is located in the X inactivation center, being transcribed from the inactive X chromosome.[163] XIST is required for the extra female X chromosome inactivation.[164] Its spreads from its site of transcription and coats the X chromosome, mediating the formation of facultative heterochromatin.[165] XIST involvement with cancer is still under investigation; however, the loss of Barr Body is a recurrent characteristic in cancer types such as breast cancer[166–170] and ovarian cancer,[170] which can be associated with the overexpression of X-linked genes, contributing to cancer progression.[171]

## Final Remarks

HPV infection is the leading cause of cervical cancer and is detected in a variety of other cancers. Its involvement with malignant transformation and tumor development has been widely investigated, mainly focusing in HPV E6 and E7 activity and their induced modulation in host's transcriptomics/proteomics. With the discovery of lncRNAs and their association with oncogenic processes in different cancers, including in viral tumors, HPV-induced modulation of host's lncRNA is starting to be investigated. In this review, we discussed the initial research work in this field as mitochondrial lncRNAs and MALAT-1 that were shown to have altered expression by HPV proteins, affecting cell proliferation. More importantly, we deeply explored published papers that performed gene expression microarrays to search annotated lncRNAs altered by HPV infection, activity, or HPV protein expression (Table 1). Among genes presented in Table 1, some lncRNAs, such as MALAT1, H19, and MEG3, are extensively involved in oncogenic processes and may play an essential role in HPV-induced carcinogenesis and, in the future, they may arise as potential targets for therapeutic treatment, diagnosis, or prognosis factors.

## Author Contributions

Conceived the manuscript: LG. Wrote the first draft of the manuscript: LG, JRP, EMN, GND, and EME. Contributed to the writing of the manuscript: LG, JRP, EMN, GND, and EME. Jointly developed the structure and arguments for the paper: LG, JRP, EMN, GND, and EME. Made critical revisions and approved the final version: LG, JRP, EMN, GND, and EME. All authors reviewed and approved the final manuscript.

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