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Review

Role of lncRNA Alterations in Cervical Oncogenesis

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Abstract

Objectives: Human Papillomavirus (HPV) is the main contributor to the development of cervical cancer. This study aimed to investigate the biological significance of changes in the expression of lncRNAs induced by HPV oncoproteins in cervical oncogenesis mechanisms.

Methods: We performed a review using online databases. The alterations were associated with some molecular and/or cellular characteristics that could be involved in the pathogenesis of cervical cancer. The molecular targets of the RNAs were identified using the Gene Expression Profiling Interactive Analysis (GEPIA) bioinformatics sites/tools, GeneCards®, OMIM, and Lnc2Cancer 3.0.

Results: Sixty-one altered lncRNAs were identified. The alterations contribute to the higher staging of cervical cancer and a worse prognosis. These lncRNAs can act by competing for miRNAs for response elements, influencing the regulation of target genes and, ultimately, participating in the cancer regulation process and exhibit multiple biological functions, such as chromatin modification, transcription, translation, splicing, and epigenetic regulation.

Conclusion: Changes in lncRNA expression have been associated with the onset, progression, and prognosis of cervical cancer. These changes can contribute to several features of cervical oncogenesis, and their identification has the potential to provide new biomarkers and therapeutic targets for the treatment of this cancer.

Keywords: Cervical cancer, HPV Human Papillomavirus, Long Noncoding, Oncogenesis, RNA

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Cervical cancer is considered a public health problem, representing the third most frequent and fourth cause of mortality among women in Brazil. In world statistics, it is also among the first related to cancer processes in women, especially in developing countries.[1-3]

Long-term infection by Human Papillomavirus (HPV), especially those at high risk (especially HPV 16 and HPV 18), is the main etiological contributor to the development of cervical cancer, having been observed in 99.7% of all cases of cervical cancer.[3-11]

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Viral oncogenes E6 and E7 are consistently overexpressed after HPV genome incorporation into host cell DNA. Its incorporation leads to a series of oncogenic advances. The best-studied and known advances are induction of tumor suppressor protein p53 degradation by the viral oncoprotein E6 and cellular transformation through interaction with the PDZ domain of cellular proteins and pRb led by oncoprotein E7. The HPV16 E6/E7 proteins can also increase the expression of the polycomb repressive complex 2 (PRC2) and the methyltransferase enhancer of zeste homolog 2 (EZH2) at the level of messenger RNA (mRNA) and protein, which modify gene expression through increased histone H3 Lys27 trimethylation.[8,10,12,13]

Recent studies have associated changes in expression levels of non-coding RNA molecules, such as long non-coding RNAs (lncRNAs), induced by HPV as another possible pathogenic pathway important for neoplastic process development.[14,15]

Long non-coding RNAs (lncRNAs) are a class of ribonucleic acid (RNA) molecules with more than 200 nucleotides in length that do not encode proteins. They play important roles in several cellular activity regulations, such as epigenetic regulation, silencing of chromosomes, chromatin modification, transcriptional activation, post-transcriptional regulation, protein regulation, and can be used as "sponges" competitively inhibiting microRNAs (miRNAs).[7,16-18] Growing evidence has established the potential relationship between dysregulation of lncRNA expression and numerous human diseases such as cancer, metabolic diseases, neurodegenerative and psychiatric diseases, and immune dysfunction.[18-22]

Numerous studies show that they play vital roles in the progression and development of various human neoplasms. The expression of lncRNAs is different in distinct tissues, and its expression may be increased or reduced. lncRNAs dysfunction is involved in tumorigenesis, from proliferation to resistance to apoptosis, angiogenesis, and metastasis. They can act as important biomarkers and potential drug targets for various types of cancer, and the regulation of lncRNA expression can influence tumor development and progression.[7,8,21,23-25]

Changes in the expressiveness of lncRNAs are associated with the emergence, progression, and prognosis of different types of cancer, including cervical cancer.[7,8,10] Also, HPV can compromise the expressiveness rates of different types of lncRNAs, with biological consequences in the onset, progression, and prognosis of cervical cancer.[9]

Therefore, this study aimed to carry out a survey, through a review of specialized literature, the contribution of lncRNAs with altered expression levels with the "Hallmarks" of cervical cancer, through the analysis of mechanisms of action promoted by varying levels of expressiveness in the pathogenesis of cervical cancer, verifying the biological significance of expression in the onset, progression, and prognosis of the disease.

Methods

The study was developed based on an integrative literature review, using the PubMed/MEDLINE, SCOPUS, Web of Science, RevMan databases, from October 2018 to December 2020. The descriptors used for selecting the articles related to the subject were: cervical cancer, long non-coding RNA (lncRNA), HPV, and oncogenesis using the Boolean operator "AND". This strategy allowed the retrieval of 341 articles, but only those published in the last ten years about correlations inherent to the expression of lncRNAs induced by HPV in the pathogenesis of cervical neoplasms were selected, excluding literature reviews, thus a total of 128 full articles were selected.

The articles were organized in a spreadsheet according to the correlation between the lncRNAs expression level and the development of cervical cancer. In addition, we observed the relationship between the expressiveness of lncRNAs in HPV infection. We verified the mechanisms by which these lncRNAs would contribute to the hallmarks of oncogenesis, comparing normal cervical tissues and tissues compromised by cervical cancer infected by the virus.

The identification of molecular targets of these RNAs occurred using the Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/), GeneCards® (https://www.genecards) sites/bioinformatics tools. org/), OMIM (https://www.omim.org/), and Lnc2Cancer 3.0 (http://www.bio-bigdata.com/lnc2cancer/), which also allowed to exclude the duplicated lncRNA count due to distinct nomenclature used in the studies, since, in the platforms, the different synonyms for lncRNAs were presented.

Results and Discussion

We identified sixty-one different types of lncRNA with altered expression levels correlated with oncogenic processes in cervical cancer. Some of these had well-defined mechanisms of action, however, others are still unknown. We observed a predominance in the number of lncRNA with increased expression levels (Fig. 1). Among the lncRNAs found, 44 showed increased expression, showing to be strongly correlated with HPV infections.

lncRNAs can regulate gene expression at different levels and are widely involved in various physiological and pathological processes. Dysregulation in the expression level of these lncRNAs is associated with the development and pro-

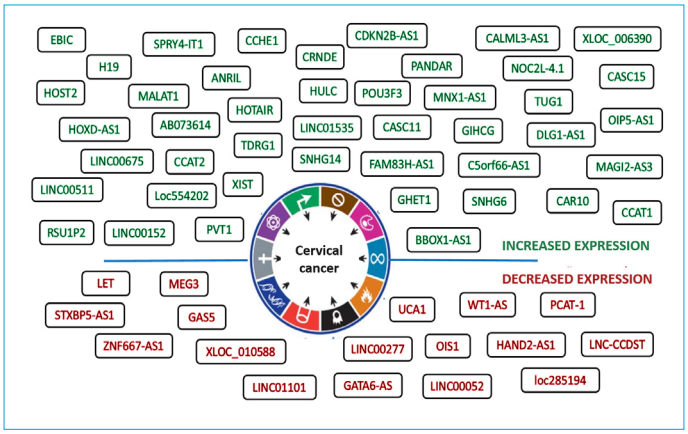

Figure 1. Analyzed lncRNAs with altered expression levels in cervical cancer tissues.

Source: Adapted from HANAHAN & WEINBERG, 2011.[26]

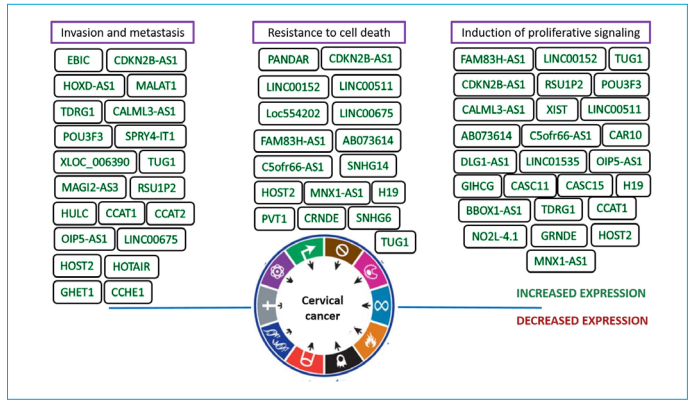

Figure 2. lncRNAs with increased expression levels analyzed with hallmarks of uterine cervix carcinogenesis.

Source: Adapted from HANAHAN & WEINBERG, 2011.[26]

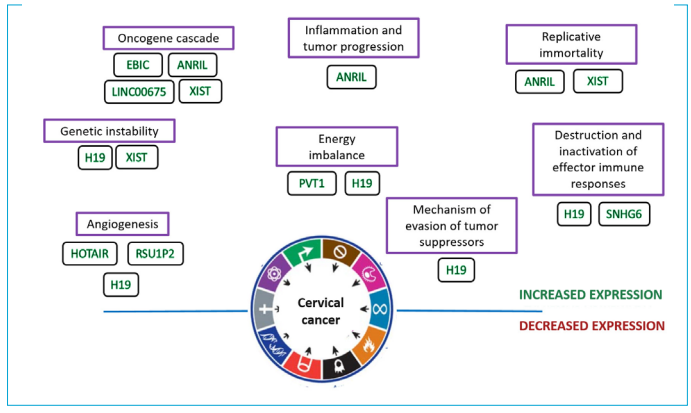

Figure 3. lncRNAs with increased expression levels analyzed with hallmarks of uterine cervix carcinogenesis. Cont.

Source: Adapted from HANAHAN & WEINBERG, 2011.[26]

gression of cervical cancer through different mechanisms. One of the most cited mechanisms/hypotheses was that it acts as an endogenous competitive RNA, affecting the regulation of miRNAs in the mRNA of the target gene.

Experimental studies pointed out, in the 61 verified lncRNAs, a direct association with the carcinogenic process. Of these, 55 lncRNAs had the mechanisms of action verified, and six lncRNAs only had the identification of the alteration in the expression level in cervical carcinogenesis indicated, suggesting further analysis to recognize their mechanism of action.

Some lncRNAs, such as HULC, CCAT2, SPRY4-IT1, and GHET1, showed high expression levels. However, the mechanisms by which they contribute to the tumorigenesis process is not clear. The participation of these lncRNAs has been reported in biological and cellular processes in cancer, such as cell growth, metastases, and cell differentiation, with high levels indicated as an independent prognostic factor for overall survival in patients with cervical cancer (Table 1, Figs. 2 and 3).[5,27,28]

LncRNAs such as PVT1, HOST2, H19, LINC00152, LINC01535, POU3F3, TDRG1, CDKN2B-AS1, XIST, GIHCG, C5ofr66-AS1, DLG1-AS1, MAGI2-AS3, OIP5-AS1, SNHG6, NOC2L-4.1, BBOX1-AS1, CAR10, CCAT1, RSU1P2, and XLOC_006390 can perform their mechanism of action through miR inactivation, in addition to contributing to the instability of protein complexes.[12,23,29,30,32,33,58] The endogenous RNA hypothesis explained most of the actions of lncRNAs with accentuated levels of expression, from which competitive mechanisms of binding with miRNAs were observed, affecting the regulation of miRNA in the mRNA of the target gene. Like a molecular sponge, lncRNAs inhibited miRNAs and thus could interact and influence transcription factors. Furthermore, by their action as ceRNAs, lncRNAs can regulate the distribution of molecules in the miRNA and, therefore, impose an additional level of post-transcriptional regulation.[16,18-20,22]

The concept that programmed cell death by apoptosis serves as a natural barrier to cancer development was established a few decades ago. High levels of oncogenes provided an imbalance in different signaling pathways, thus leading to cell hyperproliferation. Intra and extracellular regulatory mechanisms can initiate proteolysis by activating latent proteases, such as caspases, which lead to the proteolytic cascade. The "apoptotic trigger" that transmits signals between regulators and effectors is controlled by the regulatory proteins of the Bcl-2 family.[59]

Identified lncRNAs such as PANDAR, CDKN2B-AS1, LINCOO152, LINC00511, Loc554202, LINC00675, FAM83H-AS1, AB073614, C5ofr66-AS1, SNHG14, HOST2, MNX1-AS1, H19, PVT1, CRNDE, SNHG6, and TUG1 can modulate apoptosis and thus resist cell death. Once cell death is unfeasible, the

Table 1. Up-regulated lncRNAs and their mechanisms of action.

lncRNA (Reference)	Mechanism	Cancer
Hallmark		
MALAT1[42]	EZH2 enzyme binding	Invasion and metastasis.
SPRY4-IT1[5]	Unknown	
HOXD-AS1[8]	Ras/ERK Signaling	
CCHE1[24]	Ras/ERK Signaling	
MAGI2-AS3[43]	CDK6 up-regulation by action on miR-320 and miR-186	
GHET1[44]	Unknown	
CCAT2[28]	Unknown	Resistance to cell death.
Loc554202[7]	Protein binding	
CRNDE[39]	Apoptosis modulation via p53	
SNHG14[40]	Activation of the JAK-STAT signaling pathway	
MNX1-AS1[45]	Increased expression of p-ERK1 and p-JNK	
DLG1-AS1[16]	MiR-107 inhibition removal	Induction of proliferative signaling.
LINC01535[46]	Inhibition of miR-124 and release from the EZH2 pathway	
CASC11[47]	β-catenin activation	
CASC15[48]	Modulation of the epithelial-mesenchymal transition	
GIHCG[31]	miR-200b inactivation	
NOC2L-4.1[49]	miR-630 inhibition	
BBOX1-AS1[50]	miR-361-3p inhibition	
CAR10[18]	miR-125b-5p inhibition and PDPK1 positive regulation	
EBIC[51]	EZH2 enzyme binding and inhibition of E-cadherin expression	Invasion and metastasis; Oncogene cascade
HULC[27]	Unknown	Invasion and metastasis; angiogenesis
SNHG6[41]	miR-485-3p inhibition	Destruction and inactivation of effector immune responses; resistance to cell death.
POU3F3[52]	MiR-127-5p / FOXD1 axis regulation	Induction of proliferative signaling; invasion and metastasis.
CCAT1[22]	miR-181a inhibition	
TDRG1[30]	miR-326 inactivation	
CALML3-AS1[53]	β-catenin activation	
OIP5-AS1[54]	Inhibition of miR-143-3p and modulation of ROCK1 expression	
C5orf66-AS1[17]	miR-637 inactivation	Induction of proliferative signaling; resistance to cell death.
AB073614[37]	RBMS gene inhibition	
LINC00511[38]	Protein binding	
LINC00152[55]	MiR-216b-5p/HOXA1 axis regulation	
CDKN2B-AS1[33]	Inactivation of miR-181a-5p/TGFβ1 axis	
FAM83H-AS1[36]	Regulation via E6-p300 independent of p53	
TUG1[6]	Protein binding	Resistance to cell death; induction of proliferative signaling; invasion and metastasis.
HOST2[32]	miR let-7b inactivation	
PVT1[23,56,12]	miR-195 interaction and protein binding	Energy imbalance; resistance to cell death.
ANRIL[57,33]	Modulation of the epithelial-mesenchymal transition	Oncogene cascade; inflammation and tumor progression; replicative immortality.
H19[34]	EZH2 enzyme binding, p53 suppression and miR-675 inactivation	Mechanism of evasion of tumor suppressors; genetic instability; energy imbalance; induction of proliferative signaling; angiogenesis; resistance to cell death; destruction and inactivation of effector immune responses.
XIST[29]	miR-140-5p inactivation and activation of the ORC1 pathway	Induction of proliferative signaling; genetic instability; oncogene cascade; replicative immortality.
LINC00675[35]	β-catenin activation	Resistance to cell death; oncogene cascade; invasion and metastasis.
RSU1P2[19]	Inhibition of miR-let7a and regulation of transcription factors IGF1R, N-myc and EphA4	Angiogenesis; induction of proliferative signaling; invasion and metastasis.

damaged cell will present a prolonged period of permanence and replication of its error, thus enabling the evolution of dysplastic events that compromise the uterine tissue.[6,7,9,12,17,32-41,58]

Bcl-2, an integral protein, is located in the mitochondrial membrane and has anti-apoptotic properties. When stimulated by apoptotic signals, cytochrome C is released into the mitochondrial cytosol, then binds to Apaf-1 and activates caspase-like protease to bring about rapid and irreversible apoptosis. Decreased susceptibility of cells to death is associated with a high proportion of Bcl-2. Thus, the apoptotic effect of these lncRNAs in cervical cancer could be mediated by the mitochondrial pathway, where resistance to cell death would be the primary hallmark of the contribution of these lncRNAs in oncogenic mechanisms.[7,59]

Infection with high-risk HPVs leads to the development of precancerous lesions in the cervix. Oncogenesis only occurs as the result of additional genomic and epigenomic changes in these cells, as HPV infection alone is insufficient to trigger the development of cervical cancer. HPV overexpresses E6 and E7 oncoproteins to disrupt the normal function of the tumor suppressor gene in the host. After integration, viral proteins begin to damage host cells.[36,60]

In HPV-related cancer, viral proteins E6/E7 interrupt cell cycle checkpoint control by both cyclin-dependent kinase (CDK) inhibitors (p21, p27, p16) and degradation of p53 and pRb. Degradation of p53 by the E6 oncoprotein inhibits apoptosis and allows cells to continue replicating. HPV benefits from this damage-response pathway for its replication and produces large numbers of episomal HPV, required for the viral DNA to integrate into the host genome. Thus, the degradation of pRb by the E7 oncoprotein will cause entry into the S phase of the cell cycle that eventually promotes cell proliferation. Viral replication requires the cell to enter the S phase of the cell cycle. This is achieved by inactivating pRb and releasing transcription factors from the transcription factor family (E2F) that allow cell progression through the cycle at the G1 checkpoint.[61-63]

Modulation of the epithelial-mesenchymal transition (EMT) was also observed as a mechanism of action for different types of lncRNA, such as ANRIL, CASC15, and HOTAIR. These are capable of acting on the PI3K/Akt pathway, providing the occurrence of lymph node metastases and a more advanced stage of the disease.[48,57,64] HOTAIR is also able to interact with PCR2 and LSD1 acting on gene silencing, another important pathway contributing to the evolution of the neoplastic process.[65-67] Through EMT, transformed cells can acquire abilities to invade, resist apoptosis, and spread. EMT-inducing transcription factors have therefore been identified as capable of orchestrating most steps of the invasion-metastasis cascade.[5,6,12,25,57]

Like normal tissues, tumors require sustenance (nutrients and oxygen) and the ability to evacuate waste and carbon dioxide. Some angiogenic regulators are signaling proteins that bind to stimulatory or inhibitory cell receptors displayed by vascular endothelial cells. One of the best-known angiogenesis inducers is the vascular endothelial growth factor – A (VEGF-A). It is involved in the homeostatic growth and survival of the cellular endothelium in physiological and pathological situations. LncRNAs such as HOTAIR, RSU1P2, and H19 can stimulate VEGF-A so that the angiogenic mechanism is potentiated.[19,34,65]

On the other hand, the inflammatory process is considered a contributory aspect to tumor progression since it provides bioactive molecules to the microenvironment, including growth factors that support proliferative signaling; survival factors that limit cells to death; pro-angiogenic factors; extracellular matrix modifiers; enzymes that facilitate angiogenesis; invasion and metastasis; and inductive signals leading to EMT activation. In this scenario, the role of lncRNA ANRIL in providing inductive signals that lead to EMT activation and other facilitating programs was identified, contributing to inflammation and tumor progression.[12,57]

Seventeen lncRNAs showed reduced expression levels, highlighting their action on hallmarks such as evasion of suppressor mechanisms, invasion and metastasis, resistance to cell death, induction and proliferative signaling, and oncogene cascade (Table 2, Fig. 4).

LncRNAs such as LINC00277, LINC01101, and XLOC_010588 can interact with the HPV oncoproteins E6 and E7, inducing protein silencing mechanisms, thus providing a greater proliferative facility for cancer cells, which favors the progression of cancer and its capacity for invasion and metastasis.[10,68] In addition, although the lncRNA ZNF667-AS1 presents the induction of proliferative signaling as a primary mechanism, the pathways that contribute to cancer progression have not yet been identified. However, its lower level of expression, when compared to normal tissues, has been identified.[25] Among the lncRNAs with reduced expression level, most of them presented as an identified mechanism of action the interaction with different types of miRNA, resulting in the infeasibility of tumor growth inhibition, invasion and metastasis, and promotion of apoptotic events. Within this course of action, the following stand out: MEG3, GAS5, WT1-AS, HAND2-AS1, and STXBP5-AS1. This possibility of action corroborates the identification of the influencing role of lncRNAs as regulatory agents in the expression of other types of non-coding RNAs, even when their expression levels are reduced, as well as in the viability of the protein synthesis they regulate (Fig. 4).

Table 2. Down-regulated lncRNAs and their mechanisms of action

lncRNA (Reference)	Mechanism	Cancer Hallmark
LET[4]	Stabilization of nuclear factor protein	Invasion and metastasis
GAS5[71, 72, 73]	miR-21 interaction	
PCAT-1[69]	Unknown	
OIS1[74]	MTK-1 regulation	
GATA6-AS[75]		
HAND2-AS1[76]	miR-330-5p inhibition	
Loc285194[70]	TGF-β1	
STXBP5-AS1[77]	miR-96-5p inhibition	
ZNF667-AS1[25]	Unknown	Induction of proliferative signaling
XLOC_010588[68]	Interaction with E6 and E7 oncogenes	
LINC01101 and LINC00277[10]		
LINC00052[78]	STAT3 repression	
UCA1[59]	β-catenin signaling	Resistance to cell death
MEG3[11]	miR-21 interaction	Mechanism of evasion of tumor suppressors
WT1-AS[79]	miR-330-5p inhibition	Oncogene cascade
lnc-CCDST[80]	Proto-oncogene DHX9	Invasion and metastasis; resistance to cell death

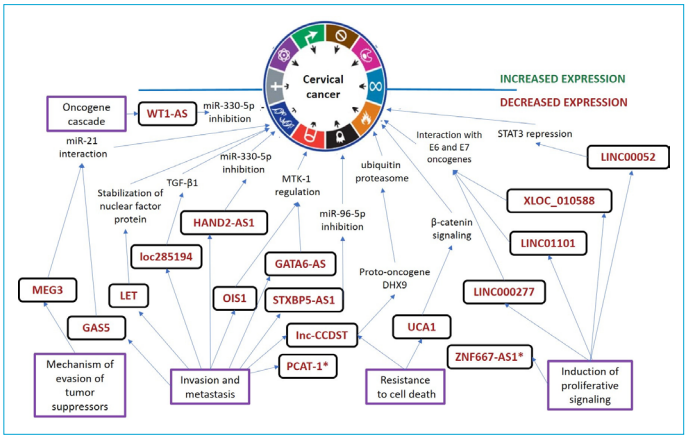

Figure 4. lncRNAs with decreased expression levels analyzed with hallmarks of uterine cervix carcinogenesis.

Source: Adapted from HANAHAN & WEINBERG, 2011.[26]

Participation in invasion and metastasis events predominated among lncRNAs with reduced expression levels, even when the pathway of action on the target gene was not identified, as occurs with PCAT-1. The signaling of the transforming factor β1 (TGF-β1) plays a central role in tumor growth and metastasis in several types of malignancies, including cervical cancer, where the action of loc285194 acting as a tumor suppressor is identified. However, their expression levels are reduced in HPV-positive tissues.[69,70] Also sharing this mechanism of action, the lncRNA LET stands out, which fails to stabilize the nuclear factor protein when induced by HPV viral oncoproteins.[4]

The action through HPV viral oncoproteins enabled the lack of control of cell-cycle proteins. Thus, preventing apoptotic events and ensuring the perpetuation of the damaged cell, a mechanism probably correlated with greater aggressiveness and worse prognosis of cervical cancer. In this scenario of resistance to cell death, the participation of UCA1 via β-catenin signaling stands out, an essential signaling pathway for controlling the development and progression of tumors.[59] In addition, the lnc-CCDST, due to the oncogenes HPV E6 and E7 action, has its expression level reduced, thus, promoting the elevation of DHX9 levels via the ubiquitin-proteasome pathway. DHX9 belongs to a family of RNA helicases with different regulatory roles in cellular processes, thus, acting as a pro-oncogenic.[80]

Conclusion

Despite progress in early diagnosis and multimodal therapies, cervical cancer incidence and mortality rates are still high. To date, no satisfactory biological markers are used routinely in cervical cancer. The involvement of lncRNAs in many biological processes and their changes in expression levels, acting at crucial points for cancer progression, such as apoptotic events, uncontrolled cell proliferative processes, and protein silencing, may contribute as important markers related to the emergence, progression, and prognosis of cervical cancer. These alterations can also be associated with HPV infection, which, due to the action of its viral oncoproteins, can compromise the expressiveness rates of different types of lncRNAs. lncRNAs act as key actors in cell differentiation, cell lineage choice,

organogenesis, and tissue homeostasis. Therefore, they can function as new biomarkers and potential pharmaceutical targets.

Due to the heterogeneity of the patient population, the early identification of new biomarkers could lead to the establishment of a more effective clinical therapy in the strategy against cervical cancer. Therefore, the focus on studies with lncRNAs is of fundamental relevance, principally when correlated with HPV infections, as this condition can lead to dysplasia of the uterine tissue, culminating in a higher incidence of cervical cancer.

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Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

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Authorship Contributions: Concept – A.L.O., T.P.P., V.D.A.; Design – A.L.O., T.P.P., V.D.A., A.E.C., V.S.N.W.; Supervision – T.A.M.F.; Materials – A.L.O., T.P.P., V.D.A.; Data collection &/or processing – A.L.O., T.P.P., V.D.A.; Analysis and/or interpretation – A.L.O., T.P.P., V.D.A., A.E.C., V.S.N.W.; Literature search – A.L.O., T.P.P., V.D.A.; Writing – A.L.O., T.P.P., V.D.A., A.E.C., V.S.N.W.; Critical review – M.F.A., E.G.C.N., W.O.P., J.V.F., T.A.M.F.

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