European Review for Medical and Pharmacological Sciences 2020; 24: 8314-8328

Long non-coding RNAs as new players in cervical carcinogenesis: an update

E.G. SALMERÓN-BÁRCENAS[1], M.A. MENDOZA-CATALÁN[2], B. ILLADES-AGUIAR[2], I. PERALTA-ARRIETA[3], I. ALQUISIRAS-BURGOS[4], J. ORTIZ-ORTIZ[2], N. NAVARRO-TITO[5], A.E. ZACAPALA-GÓMEZ[2]

[1]Laboratorio de Biomedicina Molecular, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Zacatenco, Ciudad de México (CDMX), México
[2]Laboratorio de Biomedicina Molecular, Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Guerrero, Chilpancingo, Gro, México
[3]Laboratorio de Epigenómica del Cáncer y Enfermedades Pulmonares, Unidad de Biomedicina (UBIMED), Facultad de Estudios Superiores-Iztacala, UNAM. Estado de México, México
[4]Laboratorio de Patología Vascular Cerebral, Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez", CDMX, México
[5]Laboratorio de Biología Celular del Cáncer, Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Guerrero, Chilpancingo, Gro, México

Abstract. Cervical cancer (CC) is the fourth most common cancer in women worldwide. Therefore, it is very important to understand cervical carcinogenesis, as well as the molecular mechanisms and signaling pathways involved in this process, in order to develop new strategies that contribute to diagnosis, prognosis and treatment of cervical cancer. Infection by high risk-human papillomavirus (HR-HPV) is a key event in cervical carcinogenesis, as well as, other factors, such as sociodemographics, lifestyle, sexual behavior, etc. In recent years, it has been shown that long non-coding RNA (lncRNA) are involved in CC and can be classified into tumor promoters or suppressors. Currently, several studies have analyzed the molecular mechanisms of some lncRNA in CC that might be acting, such as 1) competing endogenous RNAs (ceRNAs), 2) activators of signaling pathways, and 3) transcriptional regulators of genes. In this review, we summarized the more recent information on lncRNA and their role in the development of CC.

Key Words:
Cervical cancer, High Risk-Human Papillomavirus, Long non-coding RNA.

Introduction

During cervical carcinogenesis, the expression of several proteins involved in cell cycle/proliferation[1,2], apoptosis[3-5] and invasion/metastasis[6-8] are altered and their use as prognostic biomarkers has been proposed[6,7,9]. However, it is currently recognized that only 2% of human genome RNA encode proteins and that the majority of RNAs are transcribed into non-coding RNA[10]; interestingly, it has been estimated that 76% of the human genome is transcribed into generating thousands of long non-coding RNA (lncRNA)[11,12]. LncRNA are RNA >200 nucleotides (nt) transcribed by RNA polymerase II, do not present conserved an open reading frame (ORF) and contain a poly(A) tail, a 5-cap and a promoter region[13,14]. LncRNAs possess greater structural complexity than messenger RNA[15,16], the structural versatility of RNA allows protein recognition[17,18], metabolite sensing[19,20], competing endogenous RNA (ceRNA)[21], etc. LncRNAs are involved in the activation and inhibition of gene expression through molecular mechanisms, such as the following: a) the signal, which modulates of miRNAs regulation; b) the decoy, mRNA degradation and RNA-RNA interaction (transcriptional inhibition), and c) the guide, which participates in splicing, editing, turnover and miRNA sequestration, and the scaffold, which also participates in chromatin modification and epigenetic modification[22].

Biogenetic control of lncRNA is cell type-specific, stage-specific and lncRNA-specific, furthermore, different classes of lncRNA are transcribed from several DNA elements, such as enhancers, promoters and intergenic regions in eukaryotic genomes[22,23]. Different mechanisms are involved in the biogenesis of lncRNA, such as

Corresponding Author: Ana E. Zacapala-Gómez, Ph.D; e-mail: zak_ana@yahoo.com.mx

cleavage by ribonuclease P (RNAse P) to generate mature ends, the formation of small nucleolar RNA (snoRNA)/protein (snoRNP) complex caps at their ends, and the formation of circular structures and subnuclear structures (paraspeckles)[22].

Current research in cervical carcinogenesis focuses on lncRNA, which is a novel area at present; some studies have demonstrated the regulation, function, signaling pathways and expression of lncRNA in CC. Previous studies[12,24-27] have shown that lncRNA play a critical role in a wide range of biological processes, such as metabolism, migration, invasion, proliferation, cell cycle progression, apoptosis and metastasis. In this review, we recapitulate and summarize new and recent information on the role of the most studied lncRNA and infection by HR-HPV in cervical carcinogenesis.

Cervical Cancer

Cervical cancer (CC) is the fourth most common cancer in women, with an estimated incidence of 560,481 and 300,054 deaths annually, representing an age-standardized mortality rate of 6.8[28]. CC is preceded by precursor lesions, which are characterized by alterations in cellular differentiation, stratification and nuclear atypia, and which can be classified histologically as cervical intraepithelial neoplasia (CIN), according to the Richart classification or cytologically as squamous intraepithelial lesions (SIL) and according to the Bethesda classification[29,30], although CC is associated with sociodemographic and gynecological factors[31]. However, the most important factor comprises persistent infection with high-risk human papillomavirus (HR-HPV)[32]. A high prevalence of HPV 16 infection has been demonstrated in precancerous lesions and cervical cancer[33,34]. Specifically the E6 and E7 oncoproteins of HR-HPV induce cellular transformation by the interaction/regulation of cellular proteins, miRNA and lncRNA[35,36].

The HR-HPV E6 protein interacts with the cellular E3 ubiquitin ligase to binding E6AP to p53, resulting in the transfer of ubiquitin peptides from E6AP to p53 for its degradation by the 26S proteosome[37]. However, E6 is involved in the regulation of several processes by means of the interaction with proteins, the regulation of transcription and DNA replication (p300/CBP, Gps2, IRF-3, hMCM7, E6TP1 and ADA3); proteins involved in apoptosis and immune response evasion [Procaspase 8, Bak, TNF receptor 1 (TNF R1), FADD, and c-Myc]; proteins involved in epithelial organization and differentiation (paxillin, E6BP/ERC-55, zyxin and fibulin-1); proteins involved in cell-cell adhesion, polarity and proliferation regulation, which contain a PDZ-binding motif (NFX1, hDLG, hScrib, PKN, MAGI-1, MAGI-2, MAGI-3 or MUPP1), proteins involved in DNA repair [XRCC1 and 6-O-methylguanine-DNA methyltransferase (MGMT)][37,38] and proteins involved in cellular metabolism (HIF1-α, VHL and PI3K/AKT)[39,40]. HR-HPV E7 can interact with pRb, resulting in enhanced phosphorylation and degradation. pRb destruction leads to the release the family of E2F transcription factors and the subsequent activation of genes promoting cell proliferation. However, E7 can also regulate several cellular transcription factors (c-Myc, HIF1α, AP-1, p48, interferon regulatory factor-1 (IRF-1), forkhead transcription factor MPP2, TATA- box binding protein (TBP), TATA-box binding protein- associated factor (TAF110) and Mi2 histone deacetylase activity), proliferation (gamma-tubulin, cyclin A, cyclin E, BRCA, cyclin-dependent kinase inhibitor p21Cip1 and $p27^{kip1}$) and proteins involved in cellular metabolism (acid-α-glucosidase and pyruvate kinase M2)[37,41,42].

In relation to miRNA regulation by E6 and/or E7, miR-218 is downregulated in several HPV-16 positive cervical cancer cell lines and tissues, and this effect is mediated by the HPV-16 E6[43]. Hsa-miR-139-3p target HPV-16 oncoprotein and induces the expression of tumor suppressor proteins (p53, p21, and p16), this result in inhibition of proliferation and cell migration, cell cycle arrest at the G2-M phase and the increase of cell death in HPV-16-positive cells[44]. E6/E7 maintains the expression levels of members of the miR-17-92 cluster, which reduce the expression of *p21* anti-proliferative gene in HPV-positive cancer cells. In exosomes secreted by HeLa cells, a distinct seven-miRNA-signature was identified, with significant downregulation of let-7d-5p, miR-20a-5p, miR-378a-3p, miR-423-3p, miR-7-5p and miR-92a-3p and the upregulation of miR-21-5p, upon E6/E7 silencing[45].

Recent studies[46-52] have shown that E6 and E7 have the ability to regulate lncRNA PVT1, HOTAIR and MALAT1, which make them new players in cervical carcinogenesis. Previously, we mentioned that E6 and E7 oncoproteins can regulate lncRNAs, miRNA, mRNA and proteins[36,48,53-55], which in turn can also be regulated among themselves, interestingly, in agreement with their function lncRNA can be classified into tumor promoters and tumor suppressors.

Long Non-Coding RNA as Tumor Promoters

HOTAIR

Hox transcript antisense intergenic RNA (HOTAIR) was discovered in primary foreskin fibroblasts by tiling array. It is located in chromosome (chr) 12q13.13 in locus HOXC and encodes a 2.158 kb lncRNA[56]. Currently, eight isoforms of HOTAIR has been reported as the result of alternative splicing, alternative promoters and polyadenylation sites[57,58].

HOTAIR is up-regulated in tissues and plasma samples from patients with CC. Its expression correlates with tumor progression[59-62], and could be a diagnostic biomarker[63-65].

HOTAIR over-expression increases proliferation, cell migration, invasion and tumor growth; and decreases apoptosis *in vitro*[59,60,62,66-69]. Mechanistically, HOTAIR promotes cell migration and invasion through the downregulation of vimentin followed by the collapse of the vimentin fibers, an increase of cytoplasmatic stiffness, and the downregulation of Ubiquinol-Cytochrome C Reductase, Complex III Subunit VII (UQCRQ), which promotes mitochondrial dysfunction and increase the generation of reactive oxygen species in HeLa cells[70]. HOTAIR activates Notch, STAT3, mTOR signaling pathways and promotes the epithelial-mesenchymal transition (EMT)[61,62,71,72]. HOTAIR downregulates TET1 expression by the methylation of its promoter and significantly increases the Wnt/β catenin signaling pathway, but does not affect the mRNA level of β-catenin. Its effect is through alteration in the methylation and expression of the negative regulators (SOX17, AJAP1, MAGI2 and PCDH10) of this pathway in HeLa cells[73].

HOTAIR acting as miRNA "sponge" by direct interaction with miR-326 and miR-17-5p in HeLa, SiHa and CaSki cells[66,68]. HOTAIR promotes this cellular process through an increase of the human leukocyte antigen-G (HLA-G), mitogen-activated protein kinase 1 (MAPK1), megakaryoblastic leukemia 1 (MKL1), BCL2 (B-Cell-CLL) and Neuropilin 2 (NRP2), as well as the expression by competitively binding (ceRNA) to miR-148a[74], miR-23b[75], miR-206[76], miR-143-3p[77] and miR-331-3p[78].

HOTAIR has a single nucleotide polymorphism (SNP) in a potential enhancer located in intron 2 (rs920778) and the TT genotype correlates with HOTAIR over-expression, the risk of CC and poor prognosis in Chinese population[79]. This SNP is significantly associated with HR-HPV infection and non-response to chemo-radiotherapy[80]. The GG genotype of this SNP is associated with worse overall survival in Taiwanese population[81]. Another SNP is rs2366152, which is located in the 3' region of *HOTAIR*, a LSD1 binding domain; the TC genotype and T allele are frequent in patients with CC, low HOTAIR expression and the patients being HPV16 positive. This SNP significantly change the *HOTAIR* secondary structure and creates a binding site to miR-22, leading to its down regulation in patients with CC[82].

It is well known that in CC the main risk factor is HR-HPV infection. In this regard, HOTAIR is enriched in cervicovaginal lavage samples of patients with CC and HPV (+) infection[83]. HOTAIR expression correlates with HPV16 E7 expression in CC samples and cell lines. E7 overexpression increases HOTAIR expression in C-33A cells, It also interacts with HOTAIR to reduce the recruitment of PRC2 leading to a loss of global H3K27me3, which increases the expression of PRC2 target genes involved in metastasis in cases of CC with high levels of E7/HOTAIR[48]. The HPV16 E7/HOTAIR/miR-331-3p/NRP2 complex forms a regulator feedback loop to promote cervical carcinogenesis; E7 overexpression decreases the expression of HOTAIR, NRP2 and p53, moreover, it increases miR-331-3p expression, inhibiting the apoptosis and increasing the growth rate of MRI-H196 and MRI-H186 cells[78].

HOTAIR might be a therapeutic target, given that its downregulation decreases radio-resistance in C-33A cells via up-regulation of p21[84] and decreases the Wnt/β catenin signaling pathway, which inhibits EMT in radioresistant HeLa cells[85], while its overexpression increases resistance to radiotherapy *via* the downregulation of p21 in HeLa cells[84] and increases resistance to radiotherapy *via* upregulation of HIF-1α in HeLa and C-33A cells[86]. Recently, it was shown[87] that Bleomycin, a drug used in the treatment of CC, decreased HOTAIR expression in HeLa cells through activation of the genotoxic stress-induced intrinsic apoptotic pathway. Moreover, Artesunate, an active component from *Artemisia annua* used in Chinese traditional medicine and a semi-synthetic analog of artemisinin, inhibited HOTAIR expression, decreasing the stability and catalytic activity of COX-2, which promotes cell migration and invasion in CaSki and HeLa cells[88]. On the other hand, the anesthetic agent Propofol, decreases cell proliferation and promotes apoptosis by inhibition or the mTOR/p70S6K signaling pathway mediated by HOTAIR in C-33A, HeLa and CaSki cells[71]. Finally, HOTAIR expression increases in spheroid cervical cancer cells and promotes resistance to cisplatin-induced cytotoxicity[89] (Figure 1).

PVT1

Plasmacytoma variant translocation 1 (PVT1) was first discovered as an activator of *MYC* in murine plasmacytoma variant translocations and acts as a retroviral integration site in murine leukemia virus (MLV)-induced T lymphomas[90,91]. Fusion of the *PVT1* region and the immunoglobulin region could directly activate *MYC* by interrupting the gene itself or indirectly by disrupting protein production[92,93]. The human *PVT1* is encoded in a large locus (>30 kb) spanning 128806779-129113499, 57 kb downstream of the *MYC* gene, it is located in the chr 8q24.21 region[94-96].

PVT1 is up-regulated in tissues and serum from patients with CC; its expression is associated with the size of the tumor, advanced FIGO stage and the poor prognosis of patients with CC[52,97-100]. The PVT1 level is not changed in patients with breast cancer and ovarian cancer patients, these results suggest that PVT1 expression might be a specific diagnostic biomarker for CC and PVT1 overexpression promotes cell cycle progression, proliferation and cell migration[52,100,101].

Bioinformatics analysis and Dual-Luciferase Reporter Assays System reveal that PVT1 is targeted by several miRNA. PVT1 downregulates mir-424 expression, acting as a ceRNA in CC[98]; miR-486-3p induces ECM1 expression to promote proliferation and viability[102]; and miR-140-5p induces Smad3 expression to promote proliferation, migration and invasion[103].

PVT1 interacts with EZH2, increasing H3K27me3 levels in miR-200b and miR-195 promoters, silencing miR-200b expression to promote proliferation, cell cycle progression and migration. On the other hand, the PVT1/miR-195 axis can inhibit the response of the cancer cells to Paclitaxel *via* the regulation of EMT, HPV16 E7 knockdown also significantly inhibits PVT1 and restores miR-195 expression[50,52].

In addition, PVT1 interacts with Nucleolin, a multifunctional protein located in the cytoplasm and cell membrane, that induce ribosomal DNA transcription and regulate some oncogene expression[101], the dysregulation of cancer-related genes or their pathways is an important factor for the transformation of normal into cancer cells; once a structural or regulatory abnormality occurs, the resulting products or activity will accelerate the formation of cancer[104]. Finally, PVT1 negatively regulates TGF-β1 expression, which inhibits the growth of tumors through its antiproliferative function[99] (Figure 1).

H19

H19 was the first maternally expressed lncRNA reported (*H19/IGF2* gene cluster). *H19* was discovered in mouse fetal liver by hybridization of the cDNA library. It is transcribed from chr 11.p15.5 and encodes a 2.5 kb lncRNA[105]. H19 has two isoforms (one without part of exon 1 and another without exon 4)[106,107].

H19 expression is down-regulated in CC samples with a loss of imprinting by the usage of promoter P1 of the Insulin Like Growth Factor gene[108,109], which could be mediated by aberrant methylation in the IGF2/H19 cluster[110,111].

H19 is up-expressed in high-grade lesions (CIN3) and HeLa cells, but not in CaSki and SW756 cells, suggesting that the de-regulation of H19 expression could be an early event in cervical carcinogenesis[112]. H19 overexpression promotes proliferation by down-regulation of miR-138-5p[113], and the tumor spheroid forming ability in CC cells[114]. Finally, the C>T genotype of SNP located in exon 5 of *H19* (rs217727), is associated with the risk of CC development in Chinese population[115], while the C>T genotype of SNP (rs2839698) and the A>G genotype of SNP (rs3741219) are related to poor clinical and pathological parameters in Taiwanese population[110].

MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1 or MALAT-1), also known as nuclear-enriched abundant transcript 2 (NEAT2), is an lncRNA with a length of ~8 kb and it derives from chromosome 11q13. MALAT was first associated with high metastatic potential in patients with non-small cell lung cancer[116], however is currently associated with metastasis in several types of cancer[69,117-119].

MALAT1 expression is upregulated in tissues with CC and HeLa, SiHa and CaSki cells[26,120,121]. MALAT1 expression is correlated with tumor size, FIGO stage, vascular invasion and lymph nodes metastasis. Its expression is a predictor for poor overall survival of CC[120,122].

MALAT1 knockdown reduces proliferation, invasion, cell migration, number of colonies and apoptosis, moreover, it induces the mesenchymal-epithelial transition (MET) and cell cycle arrest[26,46,120,122,123]. A microarray analysis showed that MALAT1 knockdown upregulated 2,819 genes and downregulated 1,944 genes related to carcinogenesis (proliferation, apoptosis, transformation, etc.) in CaSki cells. MALAT1 expression is higher in HPV positive cervical cells compared

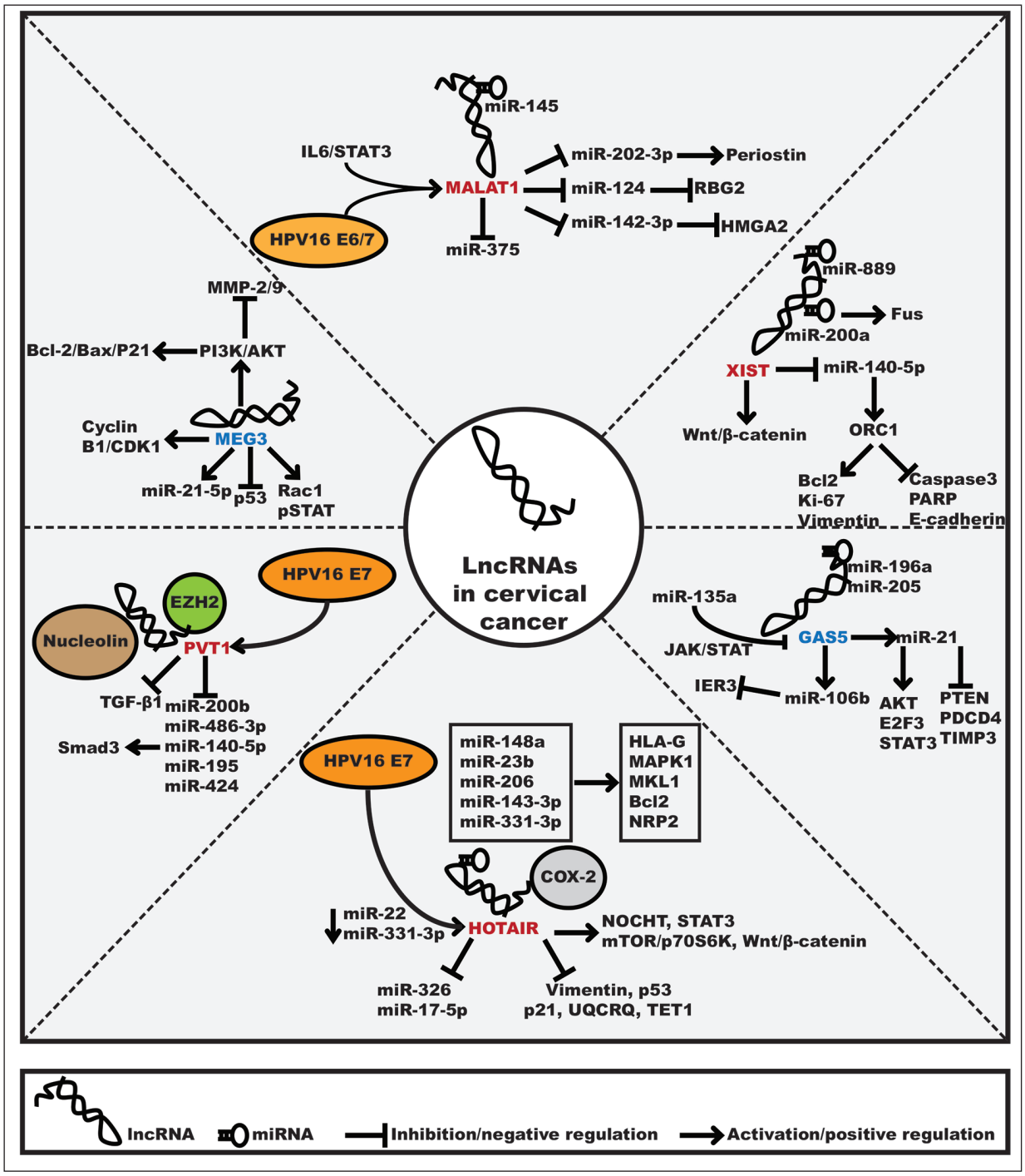

Figure 1. Molecular mechanisms of lncRNA in cervical carcinogenesis. Tumor suppressor lncRNA (Blue) inhibit onco-miRNA expression and the activation of cellular signaling pathways that promote CC. Tumor promoting lncRNA (red) inhibit tumor suppressor genes and miRNA expression, stabilize proteins through direct interaction and active cellular signaling pathways that promote CC. Ubiquinol-Cytochrome C Reductase, Complex III Subunit VII (UQCRQ),human leukocyte antigen-G (HLA-G), mitogen-activated protein kinase 1 (MAPK1), megakaryoblastic leukemia 1 (MKL1), B-Cell-CLL (BCL2), Neuropilin 2 (NRP2), Signal Transducer and Activator of Transcription 3 (STAT3), Transforming Growth Factor Beta 1 (TGF-β1), Enhancer of Zeste 2 Polycomb Repressive Complex 2 Subunit (EZH2), Ribosome-interacting GTPase 2 (RBG2), High Mobility Group AT-Hook 2 (HMGA2).

with normal cervical cells[26], promoting the cell growth and invasion of the HR-HPV-positive CC cells through the MALAT1-miR-124-RBG2 axis[47]. In the presence of HR-HPV, MALAT1 is involved in radio-resistance and its knockdown with irradiation exposure increases apoptosis, cell cycle regulation and the number of cells in G2 phase in CaSki and HeLa cells. Also, MALAT1 expression also negatively correlates with miR-145 expression, which directly interacts with the RNA-induced silencing complex (RISC) to promote miR-145 degradation[124]. In relation to HR-HPV oncoproteins, HPV16 E6 promotes MALAT1 and DNMT1 expression, decreasing miR-375 expression via methylation in SiHa and CaSki cells, in turn, miR-375 decreases cell invasion and inhibits EMT via MALAT1 downregulation in SiHa cells[125]. HPV16 E6/E7 knockdown reduces MALAT1 expression in CaSki cells[46]; in contrast, up-expression E6/E7 synergistically with IL6/STAT3 induces MALAT1 expression[126].

Periostin promotes metastatic growth by inducing cancer cell survival, invasion, and angiogenesis in several types of human cancer. Periostin expression positively correlates with MALAT1 expression and negatively correlates with miR-202-3p expression in CC; MALAT1 positively regulates the expression of periostin by negatively modulating miR-202-3p, MALAT1/miR-202-3p/periostin axis, regulating viability, cell migration, invasion and EMT in CC cells[127]. MALAT1 knockdown inhibits proliferation, invasion, tumor size, and active apoptosis by interaction with miR-429[128]. During the process of tumor metastasis, miR142-3p is significantly upregulated, whereas MALAT1 and HMGA2 are suppressed by metformin[129].

In radiotherapy, MALAT1 expression is significantly elevated compared with that of non-radiated control cells. MALAT1 knockdown enhances radiotherapy sensitivity, depresses survival percentage and cell cycle. Additionally, it enhances apoptosis in CaSki cells. Similar results are obtained by silencing miR-143/MALAT1[121], while, in treatment with Cisplatin, MALAT1 silencing promotes cisplatin-induced apoptosis in HeLa and C-33A cells[130] (Figure 1).

ANRIL

Antisense non-coding RNA in the INK4 locus (ANRIL) was discovered in the Melanoma-Neural System Tumor syndrome by sequence-tagged site real-time PCR-based gene dose mapping, long-range PCR and sequencing[131]. It is transcribed from chr 9p21 (*p15/CDKN2B-p16/CDKN2A-p14ARF* gene cluster) and encodes a 3.834 kb lncRNA[132,133].

ANRIL expression is upregulated in CC tissues and in HeLa, SiHa and CaSki cervical cancer cell lines. ANRIL expression correlates with advanced FIGO stage, lymph node metastasis and shorter overall survival[134,135]. ANRIL knockdown decreases cell migration, invasion and proliferation, and increases apoptosis in CC cell lines[135] by decreasing pPI3K/pAKT levels[134], to act as a sponge of miR-186[136] and increasing p15 expression[137].

XIST

LncRNA X-inactive specific transcript (XIST) is produced by the *XIST* gene; it is a master regulator of X inactivation in mammals[138,139]. *XIST* presents a size of 15–17 kb and is transcripted on chr Xq13[140,141]. It has six conserved regions of tandem repeats denominated A to F essentials due to its function[142,143]. XIST is known to act as scaffolding for protein recruitment, as well as an organizer of the inactive X chr (Xi) in a 3D-space[144].

In mammalian cells, one X chromosome is inactivated to achieve dosage compensation between male and female cells; XIST is important in this process. Random Xi takes place during early embryonic development and is initiated by upregulation of the *Xist* gene; Xist encodes an untranslated RNA and its accumulation in the X chromosome in cis creates a silent nuclear compartment that excludes RNA polymerase II and associated transcription factors. Upon the accumulation of Xist RNA, various proteins involved in silencing are recruited to the X chromosome; the final outcome is than the majority of genes on the Xi are stably silenced. Interestingly, some genes can escape inactivation; conditional deletion of Xist shows that, once established, Xist RNA no longer appears to be required to maintain XCI. Intriguingly, after the establishment of XCI, silenced genes remain inactive[144].

XIST overexpression in CC cells is closely related with larger tumor size, FIGO stage and distant metastasis, as well as with a low survival rate[145-148].

XIST over-expression contribute to tumor progression in CC cells by inhibiting miR-140-5p through the XIST/miR-140-5p/ORC1 axis. XIST or ORC1 knockdown suppresses cell proliferation, blocks the cell cycle and decreases the expression of Bcl-2, while increasing the apoptosis rate and the expression of c-caspase3 and cleaved PARP, improving E-cadherin expression and decreasing Ki-67 and vimentin expression in HeLa and C-33A cells[149].

XIST knockdown decreases proliferation, invasion and EMT and increases apoptosis by the up-regulation of miR-200a, which decreases Fus expression[147], decreasing the Wnt/β-catenin signaling pathway[146] and binding to miR-889-3p, decreasing miR-889-3p expression[148] (Figure 1).

NEAT1

Nuclear enriched abundant transcript 1 (NEAT1) was discovered through microarrays in WI-38 and GM00131 cells. It is transcribed from Chr11q13.1 and encodes a 3.7 kb transcript[150].

NEAT1 expression is upregulated in CC tissues and in MS751, C-33A, CaSki, HeLa, ME-180 and SiHa cell lines[151-156]. NEAT1 expression correlates with larger tumor size, poor differentiation, depth of cervical invasion, advanced FIGO stage, lymph node metastasis, and with short overall and disease-free survival[152-154].

NEAT1 overexpression promotes cell proliferation, invasion and migration[151-154]. It bound to miR-361 on order to up-regulate the expression of HSP90, thereby promoting EMT[156]. In non-sensitive tissues and radio-resistant cells (SiHa-R and HeLa-R), NEAT1 expression is increased and is more up-regulated in non-responsive patients[157]. Interestingly, NEAT knockdown exerts an effect as follows: 1) it decreases cell proliferation and migration in C-33A, SiHa, HeLa and CaSki cells through the activation of the PI3K/AKT signaling pathway and by ceRNA for miR-9-5p and miR-101[151-154], 2) it decreases cell proliferation and increases apoptosis by competitively sponging miR-193b-3p, which increases CCND1 expression in SiHa-R and HeLa-R cells, and *in vivo* [157], and 3) it decreases proliferation, colony formation, capacity of migration and invasion, also induces apoptosis due to NEAT1 negatively modulating miR-133a expression and regulating SOX4[155].

Long Non-Coding RNA as Tumor Suppressors

GAS5

Growth arrest-specific transcript 5 (GAS5) was initially identified in the cDNA library specifically from mouse NIH 3T3 cells with cycle cell arrested in G1/S phase. It is transcribed from chr 1q25 and encodes a 656 bp lncRNA[158,159]. GAS5 is spliced in two isoforms (GAS5a and GAS5b) and hosts 10 Small Nucleolar RNAs[159-161].

GAS5 expression is downregulated in CC tissues and in HeLa, C-33A, CasKi, SiHa, HT-3, SW756 and ME-180 cell lines. GAS5 down-regulation is associated with advanced FIGO stage, vascular invasion, lymph node metastasis and poor prognosis in patients with CC[69,162-164].

GAS5 knockdown increases cell migration, invasion and proliferation[69,162,163] and decreases apoptosis by the up-regulation of miR-21, phosphorylatio E2F3 and STAT3 and the down-regulation of TIMP3 and PDCD4 in HeLa and SiHa cells[165].

Conversely, GAS5 overexpression decreases cell viability, anchorage-independent growth and invasion, and increases apoptosis by acting as a molecular sponge of miR-196a and miR-205 in SiHa and ME-180 cells. Moreover, it decreases tumor growth *in vivo* through the downregulation of miR-196a, miR-205[166] and miR-21 expression, which increases PTEN and PDCD4 expression and inhibits proliferation, cell migration and invasion in HeLa, SiHa and CaSki cells[164]. GAS5 is targeted by miR-135a through the JAK/STAT signaling pathway that participates in the development of CC. GAS5 overexpression inhibits proliferation, cell cycle, migration, invasion, EMT and tumor growth and metastasis (nude mice), also activates apoptosis[167,168].

GAS5 expression could be a therapeutic target. Its overexpression increases sensitivity to cisplatin-induced apoptosis[165], decreases miR-106b expression, which increases IER3 expression[169] and decreases tumor growth *in vivo* and the pAKT level, which decreases the survival of SiHa/cDDP cells and cisplatin-resistant CC cells[164].

The hypermethylation of GAS5 induce its downexpression in CC tissues as well as in HeLa, SiHa, CaSki and C-33A cells[168], and finally, to the down expression of GAS5 in HEKa cells transfected with E6[170] (Figure 1).

MEG3

The maternally expressed gene 3 (MEG3) is a maternally expressed imprinted lncRNA. *MEG3* was discovered in normal fertilized embryos by subtraction and hybridization. *MEG3* is transcribed from Chr14q32 and encodes a ~7 kb lncRNA[171]. Twelve isoforms has been reported of MEG3 in human fetal liver identified by RT-PCR and sequencing. These isoforms stimulate p53-mediated transactivation and decrease DNA synthesis in HCT116 cells[172]. The *MEG3* gene is the host gene for miR-770 tumor suppressor[173].

MEG3 expression is down-regulated in CC tissues and in C-33A, C4-1, CaSki, SiHa and HeLa cell lines[174,175]. MEG3 expression is decreased in the exosomes of cervicovaginal lavage speci-

mens with CC patients compared with those of patiens who are HPV-positive and HPV-negative, cancer-free patients[83]. On the other hand, *MEG3* methylation is increased in the plasma and tissue of patients with CC compared with healthy volunteers. The ROC curve analysis showed that this could be useful as a diagnostic biomarker, and Kaplan-Meier plots revealed that the hypermethylation of *MEG3* was associated with poorer recurrence-free survival and overall survival. These data suggest that *MEG3* methylation in plasma and tissues from patients with CC can serve as a diagnostic and prognostic biomarker in CC[176,177]. Methylation in *MEG3* promoter is increased in patients with CC and cell lines (HeLa and CaSki); the de-methylation of the *MEG3* promoter increases its expression, decreasing cell proliferation in HeLa and CaSki cells[176].

MEG3 overexpression gives rise to the following: 1) it inhibits proliferation, cell migration and invasion, and induces cell cycle arrest at the G2/M phase and apoptosis through p53 and the cyclin B1-CDK 1 signaling pathway in HeLa and C-33A cells[175], 2) it decreases cell proliferation and increases apoptosis by the downregulation of miR-21-5p in HeLa and CaSki cells[178]; 3) it decreases cell invasion and proliferation by the downregulation of Rac1 in HeLa cells[174] and by promoting the degradation of pSTAT[179]; and 4) it decreases cell proliferation, invasion and migration, and increases apoptosis/ cell cycle arrest at the G1 phase by the down-regulation of PI3K, AKT, Bcl-2, and MMP-2/9, as well as the up-regulation of Bax and P21 in HeLa cells[180]. Finally, Lidocaine inhibits cell viability and apoptosis by inducing the expression of MEG3, which acts as a ceRNA, downregulating miR-421 expression and inducing BTG1 expression in HeLa cells[181] (Figure 1).

Other LncRNAs

Recently, it has been reported that the expression of other lncRNA are altered in CC (with <5 papers for each of these) which could acts as onco-lncRNA or tumor suppressor lncRNA. In ***Supplementary Table I,*** we summarized the main characteristics, such as expression level (up or down-regulated), samples analyzed (tissues or cell lines), association with clinicopathological characteristics (tumor size, FIGO stage, survival, etc.), affected cell processes (migration, invasion, apoptosis, etc.) and involved molecular mechanims (activation of cell signaling pathways, acting as a molecular sponge, target genes, etc.).

Future Perspectives

The de-regulation of lncRNA is a key event in carcinogenesis and knowing more about its role will contribute to our understanding of cervical carcinogenesis. Nonetheless, little is known about many lncRNAs, which represent a new field in investigation. In this regard, it will be important to determine the following: 1) the mechanisms of de-regulation of tumor suppressor and oncogenic lncRNA (promoter hypermethylation and genomic DNA deletions); 2) the molecular mechanisms by which lncRNA suppress or promote CC (de-regulation of signaling pathways and de-regulation of tumor suppressor genes/oncogenes); 3) their importance as a therapeutic target as well of as a prognostic or diagnostic biomarker; 4) the role of lncRNA isoforms and SNP and 5) the role of HR-HPV in the de-regulation of these lncRNA, considering the role of HR-HPV E6/E7 in the regulation of lncRNAs, miRNA, mRNA and proteins expression.

Conclusions

The study of lncRNA comprises an emerging field in cervical carcinogenesis given that alteration in its expression modulates the cellular processes involved in tumor progression. These studies show that lncRNA expression might serve as prognostic or diagnostic biomarkers. Notwithstanding this, the complete understanding of the molecular mechanisms is necessary to develop drugs against novel targets in CC.

Authors' Contributions

All of the authors made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Acknowledgments

This work was performed with collaboration between Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Universidad Autónoma de Guerrero, Universidad Nacional Autónoma de México and Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez".

Conflict of Interests

The authors declare no conflicts of interest.

References

1) Wang HY, Lian P, Zheng PS. SOX9, a potential tumor suppressor in cervical cancer, transactivates p21WAF1/CIP1 and suppresses cervical tumor growth. Oncotarget 2015; 6: 20711-20722.
2) Zheng W, Zhao Z, Yi X, Zuo Q, Li H, Guo X, Li D, He H, Pan Z, Fan P, Li F, Liao Y, Shao R. Down-regulation of IFITM1 and its growth inhibitory role in cervical squamous cell carcinoma. Cancer Cell Int 2017; 17: 88.
3) Chen M, Zhang Y, Zheng PS. Tafazzin (TAZ) promotes the tumorigenicity of cervical cancer cells and inhibits apoptosis. PLoS One 2017; 12: e0177171.
4) Deng H, Deng Y, Liu F, Chen J, Li Z, Zhao K, Guan X, Liang W. Stomatin-like protein 2 is overexpressed in cervical cancer and involved in tumor cell apoptosis. Oncol Lett 2017; 14: 6355-6364.
5) Moela P, Motadi LR. RBBP6: a potential biomarker of apoptosis induction in human cervical cancer cell lines. Onco Targets Ther 2016; 9: 4721-4735.
6) Wang J, Ou J, Guo Y, Dai T, Li X, Liu J, Xia M, Liu L, He M. TBLR1 is a novel prognostic marker and promotes epithelial-mesenchymal transition in cervical cancer. Br J Cancer 2014; 111: 112-124.
7) Zacapala-Gomez AE, Navarro-Tito N, Alarcon-Romero LDC, Ortuno-Pineda C, Illades-Aguiar B, Castaneda-Saucedo E, Ortiz-Ortiz J, Garibay-Cerdenares OL, Jimenez-Lopez MA, Mendoza-Catalan MA. Ezrin and E-cadherin expression profile in cervical cytology: a prognostic marker for tumor progression in cervical cancer. BMC Cancer 2018; 18: 349.
8) Zhang WN, Li W, Wang XL, Hu Z, Zhu D, Ding WC, Liu D, Li KZ, Ma D, Wang H. CLDN1 expression in cervical cancer cells is related to tumor invasion and metastasis. Oncotarget 2016; 7: 87449-87461.
9) Ouyang F, Liu J, Xia M, Lin C, Wu X, Ye L, Song L, Li J, Wang J, Guo P, He M. GINS2 is a novel prognostic biomarker and promotes tumor progression in early-stage cervical cancer. Oncol Rep 2017; 37: 2652-2662.
10) Frith MC, Pheasant M, Mattick JS. The amazing complexity of the human transcriptome. Eur J Hum Genet 2005; 13: 894-897.
11) Zhao M, Qiu Y, Yang B, Sun L, Hei K, Du X, Li Y. Long non-coding RNAs involved in gynecological cancer. Int J Gynecol Cancer 2014; 24: 1140-1145.
12) Peng L, Yuan X, Jiang B, Tang Z, Li GC. LncRNAs: key players and novel insights into cervical cancer. Tumour Biol 2016; 37: 2779-2788.
13) Ernst C, Morton CC. Identification and function of long non-coding RNA. Front Cell Neurosci 2013; 7: 168.
14) Zhang Y, Yang L, Chen LL. Life without a tail: new formats of long noncoding RNAs. Int J Biochem Cell Biol 2014; 54: 338-349.
15) Clark MB, Johnston RL, Inostroza-Ponta M, Fox AH, Fortini E, Moscato P, Dinger ME, Mattick JS. Genome-wide analysis of long noncoding RNA stability. Genome Res 2012; 22: 885-898.
16) Wan Y, Qu K, Ouyang Z, Kertesz M, Li J, Tibshirani R, Makino DL, Nutter RC, Segal E, Chang HY. Genome-wide measurement of RNA folding energies. Mol Cell 2012; 48: 169-181.
17) Lehmann K, Schmidt U. Group II introns: structure and catalytic versatility of large natural ribozymes. Crit Rev Biochem Mol Biol 2003; 38: 249-303.
18) Wu Q, Huang L, Zhang Y. The structure and function of catalytic RNAs. Sci China C Life Sci 2009; 52: 232-244.
19) Cech TR. Ribozymes, the first 20 years. Biochem Soc Trans 2002; 30: 1162-1166.
20) Serganov A, Patel DJ. Metabolite recognition principles and molecular mechanisms underlying riboswitch function. Annu Rev Biophys 2012; 41: 343-370.
21) Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell 2011; 146: 353-358.
22) Dahariya S, Paddibhatla I, Kumar S, Raghuwanshi S, Pallepati A, Gutti RK. Long non-coding RNA: Classification, biogenesis and functions in blood cells. Mol Immunol 2019; 112: 82-92.
23) Spurlock CF, 3rd, Crooke PS, 3rd, Aune TM. Biogenesis and transcriptional regulation of long noncoding RNAs in the human immune system. J Immunol 2016; 197: 4509-4517.
24) Liu Y, Yang Y, Li L, Geng P, Li G, Song H. LncRNA SNHG1 enhances cell proliferation, migration, and invasion in cervical cancer. Biochem Cell Biol 2018; 96: 38-43.
25) Shi D, Zhang C, Liu X. Long noncoding RNAs in cervical cancer. J Cancer Res Ther 2018; 14: 745-753.
26) Sun R, Qin C, Jiang B, Fang S, Pan X, Peng L, Liu Z, Li W, Li Y, Li G. Down-regulation of MALAT1 inhibits cervical cancer cell invasion and metastasis by inhibition of epithelial-mesenchymal transition. Mol Biosyst 2016; 12: 952-962.
27) Shang C, Wang W, Liao Y, Chen Y, Liu T, Du Q, Huang J, Liang Y, Liu J, Zhao Y, Guo L, Hu Z, Yao S. LNMICC promotes nodal metastasis of cervical cancer by reprogramming fatty acid metabolism. Cancer Res 2018; 78: 877-890.
28) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
29) Baldwin P, Laskey R, Coleman N. Translational approaches to improving cervical screening. Nat Rev Cancer 2003; 3: 217-226.
30) Smith JH. Bethesda 2001. Cytopathology 2002; 13: 4-10.
31) Li Z, Liu F, Cheng S, Shi L, Yan Z, Yang J, Yao Y, Ma Y. Prevalence of HPV infection among 28,457 Chinese women in Yunnan Province, southwest China. Sci Rep 2016; 6: 21039.
32) zur Hausen H. Viruses as tumor initiators and tumor promoters. Haematol Blood Transfus 1985; 29: 306-307.
33) Hooi DJ, Lissenberg-Witte BI, Kenter G, de Koning MNC, Gomes Bravio I, Ardts K, Kleinmoedig S, Benita E, Pinedo HM, Berkhof J, Quint WGV, Meijer C. Human papillomavirus (HPV) prevalence and associated risk factors in women from Curacao. PLoS One 2018; 13: e0199624.
34) Thapa N, Maharjan M, Shrestha G, Maharjan N, Petrini MA, Zuo N, He C, Yang J, Xu M, Ge C, Song Z, Cai H. Prevalence and type-specific distribution of human papillomavirus infection among women in mid-western rural, Nepal- A population-based study. BMC Infect Dis 2018; 18: 338.

35) Hoppe-Seyler K, Bossler F, Braun JA, Herrmann AL, Hoppe-Seyler F. The HPV E6/E7 oncogenes: key factors for viral carcinogenesis and therapeutic targets. Trends Microbiol 2018; 26: 158-168.
36) Narisawa-Saito M, Kiyono T. Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: roles of E6 and E7 proteins. Cancer Sci 2007; 98: 1505-1511.
37) Yim EK, Park JS. The role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis. Cancer Res Treat 2005; 37: 319-324.
38) Tomaic V. Functional roles of E6 and E7 oncoproteins in HPV-induced malignancies at diverse anatomical sites. Cancers (Basel) 2016; 8: 95.
39) Guo Y, Meng X, Ma J, Zheng Y, Wang Q, Wang Y, Shang H. Human papillomavirus 16 E6 contributes HIF-1alpha induced Warburg effect by attenuating the VHL-HIF-1alpha interaction. Int J Mol Sci 2014; 15: 7974-7986.
40) Martinez-Ramirez I, Carrillo-Garcia A, Contreras-Paredes A, Ortiz-Sanchez E, Cruz-Gregorio A, Lizano M. Regulation of cellular metabolism by high-risk human papillomaviruses. Int J Mol Sci 2018; 19: 1839.
41) Nguyen CL, Eichwald C, Nibert ML, Munger K. Human papillomavirus type 16 E7 oncoprotein associates with the centrosomal component gamma-tubulin. J Virol 2007; 81: 13533-13543.
42) Roman A, Munger K. The papillomavirus E7 proteins. Virology 2013; 445: 138-168.
43) Martinez I, Gardiner AS, Board KF, Monzon FA, Edwards RP, Khan SA. Human papillomavirus type 16 reduces the expression of microRNA-218 in cervical carcinoma cells. Oncogene 2008; 27: 2575-2582.
44) Sannigrahi MK, Sharma R, Singh V, Panda NK, Rattan V, Khullar M. Role of host miRNA Hsa-miR-139-3p in HPV-16-induced carcinomas. Clin Cancer Res 2017; 23: 3884-3895.
45) Honegger A, Schilling D, Bastian S, Sponagel J, Kuryshev V, Sultmann H, Scheffner M, Hoppe-Seyler K, Hoppe-Seyler F. Dependence of intracellular and exosomal microRNAs on viral E6/E7 oncogene expression in HPV-positive tumor cells. PLoS Pathog 2015; 11: e1004712.
46) Jiang Y, Li Y, Fang S, Jiang B, Qin C, Xie P, Zhou G, Li G. The role of MALAT1 correlates with HPV in cervical cancer. Oncol Lett 2014; 7: 2135-2141.
47) Liu S, Song L, Zeng S, Zhang L. MALAT1-miR-124-RBG2 axis is involved in growth and invasion of HR-HPV-positive cervical cancer cells. Tumour Biol 2016; 37: 633-640.
48) Sharma S, Mandal P, Sadhukhan T, Roy Chowdhury R, Ranjan Mondal N, Chakravarty B, Chatterjee T, Roy S, Sengupta S. Bridging links between long noncoding RNA HOTAIR and HPV oncoprotein E7 in cervical cancer pathogenesis. Sci Rep 2015; 5: 11724.
49) Sharma S, Munger K. Expression of the cervical carcinoma expressed PCNA regulatory (CCEPR) long noncoding RNA is driven by the human papillomavirus E6 protein and modulates cell proliferation independent of PCNA. Virology 2018; 518: 8-13.
50) Shen CJ, Cheng YM, Wang CL. LncRNA PVT1 epigenetically silences miR-195 and modulates EMT and chemoresistance in cervical cancer cells. J Drug Target 2017; 25: 637-644.
51) Zhang M, Song Y, Zhai F. ARFHPV E7 oncogene, lncRNA HOTAIR, miR-331-3p and its target, NRP2, form a negative feedback loop to regulate the apoptosis in the tumorigenesis in HPV positive cervical cancer. J Cell Biochem 2018; 119: 4397-4407.
52) Zhang S, Zhang G, Liu J. Long noncoding RNA PVT1 promotes cervical cancer progression through epigenetically silencing miR-200b. APMIS 2016; 124: 649-658.
53) Gao D, Zhang Y, Zhu M, Liu S, Wang X. miRNA Expression Profiles of HPV-Infected Patients with Cervical Cancer in the Uyghur Population in China. PLoS One 2016; 11: e0164701.
54) Harden ME, Prasad N, Griffiths A, Munger K. Modulation of microRNA-mRNA target pairs by human papillomavirus 16 oncoproteins. mBio 2017; 8: e02170-02116.
55) Zacapala-Gomez AE, Del Moral-Hernandez O, Villegas-Sepulveda N, Hidalgo-Miranda A, Romero-Cordoba SL, Beltran-Anaya FO, Leyva-Vazquez MA, Alarcon-Romero Ldel C, Illades-Aguiar B. Changes in global gene expression profiles induced by HPV 16 E6 oncoprotein variants in cervical carcinoma C33-A cells. Virology 2016; 488: 187-195.
56) Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, Goodnough LH, Helms JA, Farnham PJ, Segal E, Chang HY. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007; 129: 1311-1323.
57) Hajjari M, Rahnama S. HOTAIR Long Non-coding RNA: characterizing the locus features by the in silico approaches. Genomics Inform 2017; 15: 170-177.
58) Li M, Li X, Zhuang Y, Flemington EK, Lin Z, Shan B. Induction of a novel isoform of the lncRNA HOTAIR in Claudin-low breast cancer cells attached to extracellular matrix. Mol Oncol 2017; 11: 1698-1710.
59) Kim HJ, Lee DW, Yim GW, Nam EJ, Kim S, Kim SW, Kim YT. Long non-coding RNA HOTAIR is associated with human cervical cancer progression. Int J Oncol 2015; 46: 521-530.
60) Huang L, Liao LM, Liu AW, Wu JB, Cheng XL, Lin JX, Zheng M. Overexpression of long noncoding RNA HOTAIR predicts a poor prognosis in patients with cervical cancer. Arch Gynecol Obstet 2014; 290: 717-723.
61) Lee M, Kim HJ, Kim SW, Park SA, Chun KH, Cho NH, Song YS, Kim YT. The long non-coding RNA HOTAIR increases tumour growth and invasion in cervical cancer by targeting the Notch pathway. Oncotarget 2016; 7: 44558-44571.
62) Li J, Wang Y, Yu J, Dong R, Qiu H. A high level of circulating HOTAIR is associated with progression and poor prognosis of cervical cancer. Tumour Biol 2015; 36: 1661-1665.
63) Sun W, Wang L, Zhao D, Wang P, Li Y, Wang S. Four circulating long non-coding RNAs act as biomarkers for predicting cervical cancer. Gynecol Obstet Invest 2018; 83: 533-539.
64) Qin S, Gao Y, Yang Y, Zhang L, Zhang T, Yu J, Shi C. Identifying molecular markers of cervical cancer based on competing endogenous RNA network analysis. Gynecol Obstet Invest 2019; 84: 350-359.

65) Zong S, Liu X, Zhou N, Yue Y. E2F7, EREG, miR-451a and miR-106b-5p are associated with the cervical cancer development. Arch Gynecol Obstet 2019; 299: 1089-1098.
66) Ji F, Wuerkenbieke D, He Y, Ding Y. Long noncoding RNA HOTAIR: an oncogene in human cervical cancer interacting with microRNA-17-5p. Oncol Res 2017;
67) Jiang Y, Li Z, Zheng S, Chen H, Zhao X, Gao W, Bi Z, You K, Wang Y, Li W, Li L, Liu Y, Chen R. The long non-coding RNA HOTAIR affects the radiosensitivity of pancreatic ductal adenocarcinoma by regulating the expression of Wnt inhibitory factor 1. Tumour Biol 2016; 37: 3957-3967.
68) Wu X, Cao X, Chen F. LncRNA-HOTAIR activates tumor cell proliferation and migration by suppressing mir-326 in cervical cancer. Oncol Res 2017;
69) Tornesello ML, Faraonio R, Buonaguro L, Annunziata C, Starita N, Cerasuolo A, Pezzuto F, Tornesello AL, Buonaguro FM. The role of microRNAs, long non-coding RNAs, and circular RNAs in cervical cancer. Front Oncol 2020; 10: 150.
70) Zheng P, Xiong Q, Wu Y, Chen Y, Chen Z, Fleming J, Gao D, Bi L, Ge F. Quantitative proteomics analysis reveals novel insights into mechanisms of action of long noncoding RNA Hox transcript antisense intergenic RNA (HOTAIR) in HeLa cells. Mol Cell Proteomics 2015; 14: 1447-1463.
71) Zhang D, Zhou XH, Zhang J, Zhou YX, Ying J, Wu GQ, Qian JH. Propofol promotes cell apoptosis via inhibiting HOTAIR mediated mTOR pathway in cervical cancer. Biochem Biophys Res Commun 2015; 468: 561-567.
72) Zhang Y, Cheng X, Liang H, Jin Z. Long non-coding RNA HOTAIR and STAT3 synergistically regulate the cervical cancer cell migration and invasion. Chem Biol Interact 2018; 286: 106-110.
73) Salmeron-Barcenas EG, Illades-Aguiar B, Del Moral-Hernandez O, Ortega-Soto A, Hernandez-Sotelo D. HOTAIR knockdown decreased the activity Wnt/beta-catenin signaling pathway and increased the mrna levels of its negative regulators in hela cells. Cell Physiol Biochem 2019; 53: 948-960.
74) Sun J, Chu H, Ji J, Huo G, Song Q, Zhang X. Long non-coding RNA HOTAIR modulates HLA-G expression by absorbing miR-148a in human cervical cancer. Int J Oncol 2016; 49: 943-952.
75) Li Q, Feng Y, Chao X, Shi S, Liang M, Qiao Y, Wang B, Wang P, Zhu Z. HOTAIR contributes to cell proliferation and metastasis of cervical cancer via targetting miR-23b/MAPK1 axis. Biosci Rep 2018; 38:
76) Zheng P, Yin Z, Wu Y, Xu Y, Luo Y, Zhang TC. LncRNA HOTAIR promotes cell migration and invasion by regulating MKL1 via inhibition miR206 expression in HeLa cells. Cell Commun Signal 2018; 16: 5.
77) Liu M, Jia J, Wang X, Liu Y, Wang C, Fan R. Long non-coding RNA HOTAIR promotes cervical cancer progression through regulating BCL2 via targeting miR-143-3p. Cancer Biol Ther 2018; 1-9.
78) Zhang M, Song Y, Zhai F. ARFHPV E7 oncogene, lncRNA HOTAIR, miR-331-3p and its target, NRP2, form a negative feedback loop to regulate the apoptosis in the tumorigenesis in HPV positive cervical cancer. J Cell Biochem 2017;
79) Guo L, Lu X, Zheng L, Liu X, Hu M. Association of long non-coding RNA HOTAIR polymorphisms with cervical cancer risk in a chinese population. PLoS One 2016; 11: e0160039.
80) Qiu H, Liu Q, Li J, Wang X, Wang Y, Yuan Z, Pei DS. Analysis of the association of HOTAIR single nucleotide polymorphism (rs920778) and risk of cervical cancer. APMIS 2016; 124: 567-573.
81) Weng SL, Wu WJ, Hsiao YH, Yang SF, Hsu CF, Wang PH. Significant association of long non-coding RNAs HOTAIR genetic polymorphisms with cancer recurrence and patient survival in patients with uterine cervical cancer. Int J Med Sci 2018; 15: 1312-1319.
82) Sharma Saha S, Roy Chowdhury R, Mondal NR, Chakravarty B, Chatterjee T, Roy S, Sengupta S. Identification of genetic variation in the lncRNA HOTAIR associated with HPV16-related cervical cancer pathogenesis. Cell Oncol (Dordr) 2016; 39: 559-572.
83) Zhang J, Liu SC, Luo XH, Tao GX, Guan M, Yuan H, Hu DK. Exosomal long noncoding RNAs are differentially expressed in the cervicovaginal lavage samples of cervical cancer patients. J Clin Lab Anal 2016; 30: 1116-1121.
84) Jing L, Yuan W, Ruofan D, Jinjin Y, Haifeng Q. HOTAIR enhanced aggressive biological behaviors and induced radio-resistance via inhibiting p21 in cervical cancer. Tumour Biol 2015; 36: 3611-3619.
85) Guo X, Xiao H, Guo S, Li J, Wang Y, Chen J, Lou G. Long noncoding RNA HOTAIR knockdown inhibits autophagy and epithelial-mesenchymal transition through the Wnt signaling pathway in radioresistant human cervical cancer HeLa cells. J Cell Physiol 2018; 234: 3478-3489.
86) Ma S, Deng X, Yang Y, Zhang Q, Zhou T, Liu Z. The lncRNA LINC00675 regulates cell proliferation, migration, and invasion by affecting Wnt/beta-catenin signaling in cervical cancer. Biomed Pharmacother 2018; 108: 1686-1693.
87) Ozgur E, Mert U, Isin M, Okutan M, Dalay N, Gezer U. Differential expression of long non-coding RNAs during genotoxic stress-induced apoptosis in HeLa and MCF-7 cells. Clin Exp Med 2013; 13: 119-126.
88) Zhang L, Qian H, Sha M, Luan Z, Lin M, Yuan D, Li X, Huang J, Ye L. Downregulation of HOTAIR expression mediated anti-metastatic effect of artesunate on cervical cancer by inhibiting COX-2 expression. PLoS One 2016; 11: e0164838.
89) Li M, Lu B, Dong X, Zhou Y, He Y, Zhang T, Bao L. Enhancement of cisplatin-induced cytotoxicity against cervical cancer spheroid cells by targeting long non-coding RNAs. Pathol Res Pract 2019; 215: 152653.
90) Graham M, Adams JM, Cory S. Murine T lymphomas with retroviral inserts in the chromosomal 15 locus for plasmacytoma variant translocations. Nature 1985; 314: 740-743.
91) Adams JM, Gerondakis S, Webb E, Corcoran LM, Cory S. Cellular myc oncogene is altered by chromosome translocation to an immunoglobulin locus in murine plasmacytomas and is rearranged similarly in human Burkitt lymphomas. Proc Natl Acad Sci U S A 1983; 80: 1982-1986.

92) Cui M, You L, Ren X, Zhao W, Liao Q, Zhao Y. Long non-coding RNA PVT1 and cancer. Biochem Biophys Res Commun 471: 10-14.
93) Siwarski D, Muller U, Andersson J, Notario V, Melchers F, Rolink A, Huppi K. Structure and expression of the c-Myc/Pvt 1 megagene locus. Curr Top Microbiol Immunol 1997; 224: 67-72.
94) Shtivelman E, Henglein B, Groitl P, Lipp M, Bishop JM. Identification of a human transcription unit affected by the variant chromosomal translocations 2;8 and 8;22 of Burkitt lymphoma. Proc Natl Acad Sci U S A 1989; 86: 3257-3260.
95) Shtivelman E, Bishop JM. Effects of translocations on transcription from PVT. Mol Cell Biol 1990; 10: 1835-1839.
96) Zhou DD, Liu XF, Lu CW, Pant OP, Liu XD. Long non-coding RNA PVT1: Emerging biomarker in digestive system cancer. Cell Prolif 50:
97) Chi S, Shen L, Hua T, Liu S, Zhuang G, Wang X, Zhou X, Wang G, Wang H. Prognostic and diagnostic significance of lncRNAs expression in cervical cancer: a systematic review and meta-analysis. Oncotarget 2017; 8: 79061-79072.
98) Gao YL, Zhao ZS, Zhang MY, Han LJ, Dong YJ, Xu B. Long noncoding RNA PVT1 facilitates cervical cancer progression via negative regulating of miR-424. Oncol Res 2017; 25: 1391-1398.
99) Wang X, Wang G, Zhang L, Cong J, Hou J, Liu C. LncRNA PVT1 promotes the growth of HPV positive and negative cervical squamous cell carcinoma by inhibiting TGF-beta1. Cancer Cell Int 2018; 18: 70.
100) Yang JP, Yang XJ, Xiao L, Wang Y. Long noncoding RNA PVT1 as a novel serum biomarker for detection of cervical cancer. Eur Rev Med Pharmacol Sci 2016; 20: 3980-3986.
101) Iden M, Fye S, Li K, Chowdhury T, Ramchandran R, Rader JS. The lncRNA PVT1 contributes to the cervical cancer phenotype and associates with poor patient prognosis. PLoS One 2016; 11: e0156274.
102) Wang C, Zou H, Chen A, Yang H, Yu X, Wang Y. C-Myc-activated long non-coding RNA PVT1 enhances the proliferation of cervical cancer cells by sponging miR-486-3p. J Biochem 2020; 167: 565-575.
103) Chang QQ, Chen CY, Chen Z, Chang S. LncRNA PVT1 promotes proliferation and invasion through enhancing Smad3 expression by sponging miR-140-5p in cervical cancer. Radiol Oncol 2019; 53: 443-452.
104) Chen Z, Xu X. Roles of nucleolin. Focus on cancer and anti-cancer therapy. Saudi Med J 2016; 37: 1312-1318.
105) Pachnis V, Belayew A, Tilghman SM. Locus unlinked to alpha-fetoprotein under the control of the murine raf and Rif genes. Proc Natl Acad Sci U S A 1984; 81: 5523-5527.
106) Lin WL, He XB, Svensson K, Adam G, Li YM, Tang TW, Paldi A, Pfeifer S, Ohlsson R. The genotype and epigenotype synergize to diversify the spatial pattern of expression of the imprinted H19 gene. Mech Dev 1999; 82: 195-197.
107) Matouk I, Ayesh B, Schneider T, Ayesh S, Ohana P, de-Groot N, Hochberg A, Galun E. Oncofetal splice-pattern of the human H19 gene. Biochem Biophys Res Commun 2004; 318: 916-919.
108) Kim SJ, Park SE, Lee C, Lee SY, Jo JH, Kim JM, Oh YK. Alterations in promoter usage and expression levels of insulin-like growth factor-II and H19 genes in cervical carcinoma exhibiting biallelic expression of IGF-II. Biochim Biophys Acta 2002; 1586: 307-315.
109) Lee C, Kim SJ, Na JY, Park CS, Lee SY, Kim IH, Oh YK. Alterations in promoter usage and expression levels of insulin-like growth factor-II and H19 genes in cervical and endometrial cancer. Cancer Res Treat 2003; 35: 314-322.
110) Huang MC, Chou YH, Shen HP, Ng SC, Lee YC, Sun YH, Hsu CF, Yang SF, Wang PH. The clinicopathological characteristic associations of long non-coding RNA gene H19 polymorphisms with uterine cervical cancer. J Cancer 2019; 10: 6191-6198.
111) Vidal AC, Henry NM, Murphy SK, Oneko O, Nye M, Bartlett JA, Overcash F, Huang Z, Wang F, Mlay P, Obure J, Smith J, Vasquez B, Swai B, Hernandez B, Hoyo C. PEG1/MEST and IGF2 DNA methylation in CIN and in cervical cancer. Clin Transl Oncol 2014; 16: 266-272.
112) Feigenberg T, Gofrit ON, Pizov G, Hochberg A, Benshushan A. Expression of the h19 oncofetal gene in premalignant lesions of cervical cancer: a potential targeting approach for development of nonsurgical treatment of high-risk lesions. ISRN Obstet Gynecol 2013; 2013: 137509.
113) Ou L, Wang D, Zhang H, Yu Q, Hua F. Decreased expression of MiR-138-5p by LncRNA H19 in cervical cancer promotes tumor proliferation. Oncol Res 2018; 26: 401-410.
114) Iempridee T. Long non-coding RNA H19 enhances cell proliferation and anchorage-independent growth of cervical cancer cell lines. Exp Biol Med (Maywood) 2017; 242: 184-193.
115) Jin T, Wu X, Yang H, Liu M, He Y, He X, Shi X, Wang F, Du S, Ma Y, Bao S, Yuan D. Association of the miR-17-5p variants with susceptibility to cervical cancer in a Chinese population. Oncotarget 2016; 7: 76647-76655.
116) Ji P, Diederichs S, Wang W, Boing S, Metzger R, Schneider PM, Tidow N, Brandt B, Buerger H, Bulk E, Thomas M, Berdel WE, Serve H, Muller-Tidow C. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene 2003; 22: 8031-8041.
117) Chen D, Liu L, Wang K, Yu H, Wang Y, Liu J, Guo Y, Zhang H. The role of MALAT-1 in the invasion and metastasis of gastric cancer. Scand J Gastroenterol 2017; 52: 790-796.
118) Chen Y, Xiao Z, Hu M, Luo X, Cui Z. Diagnostic efficacy of long non-coding RNA MALAT-1 in human cancers: a meta-analysis study. Oncotarget 2017; 8: 102291-102300.
119) Cheng Y, Imanirad P, Jutooru I, Hedrick E, Jin UH, Rodrigues Hoffman A, Leal de Araujo J, Morpurgo B, Golovko A, Safe S. Role of metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) in pancreatic cancer. PLoS One 2018; 13: e0192264.
120) Yang L, Bai HS, Deng Y, Fan L. High MALAT1 expression predicts a poor prognosis of cervical cancer and promotes cancer cell growth and invasion. Eur Rev Med Pharmacol Sci 2015; 19: 3187-3193.

121) Zhu P, Wang FQ, Li QR. Correlation study between long non-coding RNA MALAT1 and radiotherapy efficiency on cervical carcinoma and generation of radiotherapy resistant model of cancer. Eur Rev Med Pharmacol Sci 2018; 22: 5140-5148.
122) Zhang Y, Wang T, Huang HQ, Li W, Cheng XL, Yang J. Human MALAT-1 long non-coding RNA is overexpressed in cervical cancer metastasis and promotes cell proliferation, invasion and migration. J BUON 2015; 20: 1497-1503.
123) Guo F, Li Y, Liu Y, Wang J, Li G. Inhibition of metastasis-associated lung adenocarcinoma transcript 1 in CaSki human cervical cancer cells suppresses cell proliferation and invasion. Acta Biochim Biophys Sin (Shanghai) 2010; 42: 224-229.
124) Lu H, He Y, Lin L, Qi Z, Ma L, Li L, Su Y. Long non-coding RNA MALAT1 modulates radiosensitivity of HR-HPV+ cervical cancer via sponging miR-145. Tumour Biol 2016; 37: 1683-1691.
125) Liu S, Song L, Yao H, Zhang L, Xu D, Gao F, Li Q. MiR-375 is epigenetically downregulated by HPV-16 E6 mediated DNMT1 upregulation and modulates EMT of cervical cancer cells by suppressing lncRNA MALAT1. PLoS One 2016; 11: e0163460.
126) Hao Y, Yan Z, Zhang A, Hu S, Wang N, Luo XG, Ma W, Zhang TC, He H. IL-6/STAT3 mediates the HPV18 E6/E7 stimulated upregulation of MALAT1 gene in cervical cancer HeLa cells. Virus Res 2020; 281: 197907.
127) Han X, Wang Q, Wang Y, Hu B, Dong X, Zhang H, Wang W. Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1/microRNA-202-3p/periostin axis modulates invasion and epithelial-mesenchymal transition in human cervical cancer. J Cell Physiol 2019; 234: 14170-14180.
128) Shen F, Zheng H, Zhou L, Li W, Xu X. Overexpression of MALAT1 contributes to cervical cancer progression by acting as a sponge of miR-429. J Cell Physiol 2019; 234: 11219-11226.
129) Xia C, Liang S, He Z, Zhu X, Chen R, Chen J. Metformin, a first-line drug for type 2 diabetes mellitus, disrupts the MALAT1/miR-142-3p sponge to decrease invasion and migration in cervical cancer cells. Eur J Pharmacol 2018; 830: 59-67.
130) Wang N, Hou MS, Zhan Y, Shen XB, Xue HY. MALAT1 promotes cisplatin resistance in cervical cancer by activating the PI3K/AKT pathway. Eur Rev Med Pharmacol Sci 2018; 22: 7653-7659.
131) Pasmant E, Laurendeau I, Heron D, Vidaud M, Vidaud D, Bieche I. Characterization of a germ-line deletion, including the entire INK4/ARF locus, in a melanoma-neural system tumor family: identification of ANRIL, an antisense noncoding RNA whose expression coclusters with ARF. Cancer Res 2007; 67: 3963-3969.
132) Kotake Y, Nakagawa T, Kitagawa K, Suzuki S, Liu N, Kitagawa M, Xiong Y. Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15(INK4B) tumor suppressor gene. Oncogene 2011; 30: 1956-1962.
133) Yap KL, Li S, Munoz-Cabello AM, Raguz S, Zeng L, Mujtaba S, Gil J, Walsh MJ, Zhou MM. Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. Mol Cell 2010; 38: 662-674.
134) Zhang D, Sun G, Zhang H, Tian J, Li Y. Long non-coding RNA ANRIL indicates a poor prognosis of cervical cancer and promotes carcinogenesis via PI3K/Akt pathways. Biomed Pharmacother 2017; 85: 511-516.
135) Zhang WY, Liu YJ, He Y, Chen P. Down-regulation of long non-coding RNA ANRIL inhibits the proliferation, migration and invasion of cervical cancer cells. Cancer Biomark 2018; 23: 243-253.
136) Zhang JJ, Wang DD, Du CX, Wang Y. Long non-coding RNA ANRIL promotes cervical cancer development by acting as a sponge of miR-186. Oncol Res 2017; 26: 345-352.
137) Naemura M, Murasaki C, Inoue Y, Okamoto H, Kotake Y. Long noncoding RNA ANRIL regulates proliferation of non-small cell lung cancer and cervical cancer cells. Anticancer Res 2015; 35: 5377-5382.
138) Brown SD. XIST and the mapping of the X chromosome inactivation centre. Bioessays 1991; 13: 607-612.
139) Cerase A, Pintacuda G, Tattermusch A, Avner P. Xist localization and function: new insights from multiple levels. Genome Biol 2015; 16: 166.
140) Brown CJ, Ballabio A, Rupert JL, Lafreniere RG, Grompe M, Tonlorenzi R, Willard HF. A gene from the region of the human X inactivation centre is expressed exclusively from the inactive X chromosome. Nature 1991; 349: 38-44.
141) da Rocha ST, Heard E. Novel players in X inactivation: insights into Xist-mediated gene silencing and chromosome conformation. Nat Struct Mol Biol 2017; 24: 197-204.
142) Brockdorff N. X-chromosome inactivation: closing in on proteins that bind Xist RNA. Trends Genet 2002; 18: 352-358.
143) Wutz A, Rasmussen TP, Jaenisch R. Chromosomal silencing and localization are mediated by different domains of Xist RNA. Nat Genet 2002; 30: 167-174.
144) Splinter E, de Wit E, Nora EP, Klous P, van de Werken HJ, Zhu Y, Kaaij LJ, van Ijcken W, Gribnau J, Heard E, de Laat W. The inactive X chromosome adopts a unique three-dimensional conformation that is dependent on Xist RNA. Genes Dev 2011; 25: 1371-1383.
145) Kobayashi R, Miyagawa R, Yamashita H, Morikawa T, Okuma K, Fukayama M, Ohtomo K, Nakagawa K. Increased expression of long non-coding RNA XIST predicts favorable prognosis of cervical squamous cell carcinoma subsequent to definitive chemoradiation therapy. Oncol Lett 2016; 12: 3066-3074.
146) Sun G, Wang C, Zhang H. Long non-coding RNA XIST promotes cervical cancer cell epithelial-mesenchymal transition through the Wnt/beta-catenin pathway. Int J Clin Exp Pathol 2017; 10: 2333-2339.
147) Zhu H, Zheng T, Yu J, Zhou L, Wang L. LncRNA XIST accelerates cervical cancer progression via upregulating Fus through competitively binding with miR-200a. Biomed Pharmacother 2018; 105: 789-797.

148) Liu X, Xie S, Zhang J, Kang Y. Long noncoding RNA XIST contributes to cervical cancer development through targeting miR-889-3p/SIX1 axis. Cancer Biother Radiopharm 2020;
149) Chen X, Xiong D, Ye L, Wang K, Huang L, Mei S, Wu J, Chen S, Lai X, Zheng L, Wang M. Up-regulated lncRNA XIST contributes to progression of cervical cancer via regulating miR-140-5p and ORC1. Cancer Cell Int 2019; 19: 45.
150) Hutchinson JN, Ensminger AW, Clemson CM, Lynch CR, Lawrence JB, Chess A. A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. BMC Genomics 2007; 8: 39.
151) Guo HM, Yang SH, Zhao SZ, Li L, Yan MT, Fan MC. LncRNA NEAT1 regulates cervical carcinoma proliferation and invasion by targeting AKT/PI3K. Eur Rev Med Pharmacol Sci 2018; 22: 4090-4097.
152) Wang HL, Hou SY, Li HB, Qiu JP, Bo L, Mao CP. Biological function and mechanism of long noncoding RNAs nuclear-enriched abundant transcript 1 in development of cervical cancer. Chin Med J (Engl) 2018; 131: 2063-2070.
153) Wang L, Zhu H. Long noncoding nuclear paraspeckle assembly transcript 1 acts as prognosis biomarker and increases cell growth and invasion in cervical cancer by sequestering microRNA101. Mol Med Rep 2018; 17: 2771-2777.
154) Xie Q, Lin S, Zheng M, Cai Q, Tu Y. Long noncoding RNA NEAT1 promoted the growth of cervical cancer cells via sponging miR-9-5p. Biochem Cell Biol 2018;
155) Yuan LY, Zhou M, Lv H, Qin X, Zhou J, Mao X, Li X, Xu Y, Liu Y, Xing H. Involvement of NEAT1/miR-133a axis in promoting cervical cancer progression via targeting SOX4. J Cell Physiol 2019; 234: 18985-18993.
156) Xu D, Dong P, Xiong Y, Yue J, Konno Y, Ihira K, Kobayashi N, Todo Y, Watari H. MicroRNA-361-mediated inhibition of HSP90 expression and EMT in cervical cancer is counteracted by oncogenic lncRNA NEAT1. Cells 2020; 9: 632.
157) Han D, Wang J, Cheng G. LncRNA NEAT1 enhances the radio-resistance of cervical cancer via miR-193b-3p/CCND1 axis. Oncotarget 2018; 9: 2395-2409.
158) Coccia EM, Cicala C, Charlesworth A, Ciccarelli C, Rossi GB, Philipson L, Sorrentino V. Regulation and expression of a growth arrest-specific gene (gas5) during growth, differentiation, and development. Mol Cell Biol 1992; 12: 3514-3521.
159) Schneider C, King RM, Philipson L. Genes specifically expressed at growth arrest of mammalian cells. Cell 1988; 54: 787-793.
160) Gao ZQ, Wang JF, Chen DH, Ma XS, Yang W, Zhe T, Dang XW. Long non-coding RNA GAS5 antagonizes the chemoresistance of pancreatic cancer cells through down-regulation of miR-181c-5p. Biomed Pharmacother 2018; 97: 809-817.
161) Smith CM, Steitz JA. Classification of gas5 as a multi-small-nucleolar-RNA (snoRNA) host gene and a member of the 5'-terminal oligopyrimidine gene family reveals common features of snoRNA host genes. Mol Cell Biol 1998; 18: 6897-6909.
162) Cao S, Liu W, Li F, Zhao W, Qin C. Decreased expression of lncRNA GAS5 predicts a poor prognosis in cervical cancer. Int J Clin Exp Pathol 2014; 7: 6776-6783.
163) Li Y, Wan YP, Bai Y. Correlation between long strand non-coding RNA GASS expression and prognosis of cervical cancer patients. Eur Rev Med Pharmacol Sci 2018; 22: 943-949.
164) Wen Q, Liu Y, Lyu H, Xu X, Wu Q, Liu N, Yin Q, Li J, Sheng X. Long noncoding RNA GAS5, which acts as a tumor suppressor via microRNA 21, regulates cisplatin resistance expression in cervical cancer. Int J Gynecol Cancer 2017; 27: 1096-1108.
165) Yao T, Lu R, Zhang J, Fang X, Fan L, Huang C, Lin R, Lin Z. Growth arrest-specific 5 attenuates cisplatin-induced apoptosis in cervical cancer by regulating STAT3 signaling via miR-21. J Cell Physiol 2019; 234: 9605-9615.
166) Yang W, Hong L, Xu X, Wang Q, Huang J, Jiang L. LncRNA GAS5 suppresses the tumorigenesis of cervical cancer by downregulating miR-196a and miR-205. Tumour Biol 2017; 39: 1010428317711315.
167) Yan Z, Ruoyu L, Xing L, Hua L, Jun Z, Yaqin P, Lu W, Aili T, Yuzi Z, Lin M, Huiping T. Long non-coding RNA GAS5 regulates the growth and metastasis of human cervical cancer cells via induction of apoptosis and cell cycle arrest. Arch Biochem Biophys 2020; 684: 108320.
168) Yang W, Xu X, Hong L, Wang Q, Huang J, Jiang L. Upregulation of lncRNA GAS5 inhibits the growth and metastasis of cervical cancer cells. J Cell Physiol 2019; 234: 23571-23580.
169) Gao J, Liu L, Li G, Cai M, Tan C, Han X, Han L. LncRNA GAS5 confers the radio sensitivity of cervical cancer cells via regulating miR-106b/IER3 axis. Int J Biol Macromol 2019; 126: 994-1001.
170) Barr JA, Hayes KE, Brownmiller T, Harold AD, Jagannathan R, Lockman PR, Khan S, Martinez I. Long non-coding RNA FAM83H-AS1 is regulated by human papillomavirus 16 E6 independently of p53 in cervical cancer cells. Sci Rep 2019; 9: 3662.
171) Miyoshi N, Wagatsuma H, Wakana S, Shiroishi T, Nomura M, Aisaka K, Kohda T, Surani MA, Kaneko-Ishino T, Ishino F. Identification of an imprinted gene, Meg3/Gtl2 and its human homologue MEG3, first mapped on mouse distal chromosome 12 and human chromosome 14q. Genes Cells 2000; 5: 211-220.
172) Zhang X, Rice K, Wang Y, Chen W, Zhong Y, Nakayama Y, Zhou Y, Klibanski A. Maternally expressed gene 3 (MEG3) noncoding ribonucleic acid: isoform structure, expression, and functions. Endocrinology 2010; 151: 939-947.
173) Guo W, Dong Z, Liu S, Qiao Y, Kuang G, Guo Y, Shen S, Liang J. Promoter hypermethylation-mediated downregulation of miR-770 and its host gene MEG3, a long non-coding RNA, in the development of gastric cardia adenocarcinoma. Mol Carcinog 2017; 56: 1924-1934.
174) Chen X, Qu J. Long non-coding RNA MEG3 suppresses survival, migration, and invasion of cervical cancer. Onco Targets Ther 2018; 11: 4999-5007.

175) Qin R, Chen Z, Ding Y, Hao J, Hu J, Guo F. Long non-coding RNA MEG3 inhibits the proliferation of cervical carcinoma cells through the induction of cell cycle arrest and apoptosis. Neoplasma 2013; 60: 486-492.
176) Zhang J, Lin Z, Gao Y, Yao T. Downregulation of long noncoding RNA MEG3 is associated with poor prognosis and promoter hypermethylation in cervical cancer. J Exp Clin Cancer Res 2017; 36: 5.
177) Zhang J, Yao T, Lin Z, Gao Y. Aberrant methylation of MEG3 functions as a potential plasma-based biomarker for cervical cancer. Sci Rep 2017; 7: 6271.
178) Zhang J, Yao T, Wang Y, Yu J, Liu Y, Lin Z. Long noncoding RNA MEG3 is downregulated in cervical cancer and affects cell proliferation and apoptosis by regulating miR-21. Cancer Biol Ther 2016; 17: 104-113.
179) Zhang J, Gao Y. Long non-coding RNA MEG3 inhibits cervical cancer cell growth by promoting degradation of P-STAT3 protein via ubiquitination. Cancer Cell Int 2019; 19: 175.
180) Wang X, Wang Z, Wang J, Wang Y, Liu L, Xu X. LncRNA MEG3 has anti-activity effects of cervical cancer. Biomed Pharmacother 2017; 94: 636-643.
181) Zhu J, Han S. Lidocaine inhibits cervical cancer cell proliferation and induces cell apoptosis by modulating the lncRNA-MEG3/miR-421/BTG1 pathway. Am J Transl Res 2019; 11: 5404-5416.