Review

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Epigenetic mechanisms associated with progression, prognosis, and new treatment strategies for metastatic cervical squamous cell carcinoma: Literature review.

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ABSTRACT

Background: In the 21st century, the main cause of death in both sexes worldwide are cardiovascular diseases, in second place are neoplasms. In the case of women, the fourth cause of mortality is breast cancer, despite the screening. This study aims to understand the epigenetic mechanisms associated with cervical cancer progression and metastasis, considering its correlation with poor prognosis.

Material and Methods: To prepare the present article, the search was done on platforms PubMed and Google Scholar, the search was carried out using the following medical subject headings (MeSH) in the search engine: “metastatic cervical cancer”, “cervical cancer epigenetics”, “cervical cancer genetics”, “cervical cancer mirnas”, “cervical cancer lncrnas”, “cervical cancer clinical trials” and “metastatic cervical cancer hpv”, in combination with boolean connectors ‘AND’ and ‘OR’. A total of 114 articles were reviewed, published between 1989 and 2022.

Results and conclusions: It is essential to understand and know the epigenetic mechanisms associated with cervical cancer pathogenesis and progression, to create new targeted treatment schemes for metastatic cervical cancer to reduce the mortality rate and increase disease-free survival.

Keywords: metastasis, cervical cancer, lncRNA, clinical trials, targeted therapy.

INTRODUCTION:

Cervical cancer (CC) is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women after breast, colorectum, and lung cancers. Its incidence has been estimated at 604,000 new cases and its mortality at 342,000 deaths worldwide in 2020 (1). Human Papillomavirus (HPV) persistent infection is a necessary factor, observed in 99% of CC (2); however, it is not sufficient for the progression to cervical cancer (2). The main risk factors associated with CC are socio-demographic (age and education level), lifestyle behavior (diet, personal hygiene, and smoking status (3)), sexual behavior (number of sexual partners, age at sexual debut, and use of contraceptive method), gestational factors (number of pregnancies), and screening (4) and comorbidities (immunosuppressive states (5), such as Human Immunodeficiency Virus (HIV) (6), Diabetes Mellitus (DM), etc. (7,8). However, new evidence has been established as a potential risk, progression, and potential therapeutic targeted factors.

Material and Methods:

To prepare the present article, the search was done on platforms PubMed and Google Scholar, the search was carried out using the following medical subject headings (MeSH) in the search engine: "metastatic cervical cancer", "cervical cancer epigenetics", "cervical cancer genetics", "cervical cancer mirnas", "cervical cancer lncrnas", "cervical cancer clinical trials" and "metastatic cervical cancer hpv", in combination with boolean connectors 'AND' and 'OR'. A total of 114 articles were reviewed, published between 1989 and 2022. Cervical cancer pathogenesis.

Cervical cancer pathogenesis

As is known, HPV persistent infection is necessary for CC, however, it is not sufficient for CC progression. HPVs are double-stranded circular DNA viruses with an icosahedral capsid from the Papillomaviridae family. HPVs can be subdivided classically in low and high-risk HPVs depending on their association between viral genome integration (9) and anogenital cancer (10). New evidence indicates that epigenetic and genetic alterations act synergistically with HPV proteins for carcinogenesis. DNA damage is necessary for the addition of mutations; however, aberrant histone modifications can be associated with this type of cancer. DNA is coiled around by histones to form nucleosomes, the basic unit of chromosomes. The alteration of its function leads to prolonged DNA damage (11).

The association between specific HPVs and anogenital cancer has been strongly stablished. The DNA of certain high-risk HPVs, such as HPV-16, 18, 31, 33, and 39 is found in about 85% of cervical squamous cell carcinomas (CSCC) (12,13). HPV genome can be classified into three important regions: a coding region that contains early genes, E1, E2, E4, E5, E6 and E7; a region that contains genes that encode capsid proteins L1 and L2; and a non-coding region (10). HPV E6 and E7 genes are regularly expressed in HPV positive CSCC, whose are necessary for immortalization of CSCC by the interaction with tumor suppressor gene products (14). The interaction between HPV E6 protein -p53 in presence of an active ubiquitin proteolysis system leads to the specific degradation of p53 (15,16), in other words, the active degradation of negative regulator of cell growth (14). In addition, HPV E6 protein interacts with DNA methyltransferase 1 (DNMT1) (17,18), which is responsible of the methylation of cyclin A1 (CCNA1), a regulatory protein necessary for the development of CSCC (19).

The HPV E7 protein can form a specific complex with the retinoblastoma tumor suppressor gene product (p105-RB) (20), disrupting in the negative regulation of cellular growth and differentiation (21); and inhibits the activity of DNMT gene that encodes for E-cadherin protein (22) and CCL20 secretion (23) in Langerhans cells (24), its reduction may affect the efficiency by which the immune system responds to length of persistent HPV infection (25). In addition, HPV E7 protein activates the enhancer of zeste homologue 2 gene (EZH2), which encodes a polycomb group protein that interacts as a histone methyltransferase (26,27) with the regulatory function of HPV positive cancers (28) by the control of cell proliferation and it contributes to apoptotic resistance (29). The high levels of the trimethylation of lysine 27 on histone H3 (H3K27me3) by EZH2, as part of the polycomb repressive complex 2 (PRC2) contributes to progression of carcinogenesis. Another protein included as a component of the polycomb repressive complex 1 (PRC1) known as BMI1 interacts with HPV E7 protein interacting with H3K27me3, however, its specific function is already unknown (30). The demethylation of this epigenetic pathway is regulated by the KDM6A and KDM6B histone 3 lysine 27-specific demethylases, whose

remove H3K27me3 from the p16 INK4A promoter during ras/raf oncogene induced cellular senescence (31). HPV E7 protein can bind and destabilize pRB-E2F repressor complexes, allowing for uncontrolled cell cycle progression (32).

As already known, HPV persistent infection is the causal factor for cervical cancer, and the two most important proteins associated with carcinogenesis are HPV E6 and E7 proteins, whose interact with human cell proteins in gene transcription. However, the regulation of the posttranscriptional regulation is another important step in the regulation of gene transcription. In this step, there are two important epigenetic regulators, the non-coding RNAs (NcRNAs) and the RNA-binding proteins (RBPs) (33).

Cyclin dependent kinase inhibitor 2A (CDKN2A), ELAV like RNA binding protein 2 (ELAVL2), growth factor receptor bound protein 7 (GRB7), heat shock protein family B member 1 (HSPB1), KH-type splicing regulatory protein (KHSRP), polypyrimidine tract binding protein 1 (PTBP1), ribonuclease H2A (RNASEH2A), and neuro-oncological ventral antigen 1 (NOVA1) genes encode RBP proteins, and they are altered in HPV positive cancers, and are associated with the development of cervical cancer (33).

Other genetic alterations observed in CSCC demonstrated by The Cancer Genome Atlas (TCGA) project may lead to understand the signal pathways that may drive to tumorigenesis and serve as a prognostic or therapeutic markers. In cervical cancer, the number of somatic copies alterations are well stablished, amplification of telomerase RNA component (TERC, 78%), tumor protein p63 (TP63, 77%), MYC proto-oncogene (MYC, 42%), CD274 (programmed cell death 1 ligand, PD-L1, 21%), PDCD1LG2 (programmed cell death 2 ligand, PD-L2, 21%), breast cancer anti-estrogen resistance 4 (BCAR4, 20%), KLF transcription factor 5 (KLF5, 18%), epidermal growth factor receptor (EGFR, 17%), baculoviral IAP repeat containing 2/3 (BIRC2/3, 17%), and erb-b2 receptor tyrosine kinase 2 (ERBB2, 17%); recurrent deletions of transforming growth factor beta receptor 2 (TGFBR2, 36%), FAT atypical cadherin 1 (FAT1, 36%), phosphate and tensin homolog (PTEN, 31%), and SMAD family member 4 (SMAD4, 28%) genes, were the most prevalent. (34) The molecular mechanisms, such as DNA mutations, and their respective signaling pathways are observed in CSCC carcinogenesis, as seen in Figure 1, which shows the upregulation or downregulation of their respective metabolic pathways, and if exists an associated specific targeted therapy.

Epigenetic mechanisms associated with metastasis

Epigenetic mechanisms are associated with multiple metabolic pathways; however, currently new evidence has aroused interest in how such mechanisms are associated with proliferation, invasion, and metastasis in cancer (35). There are some genome regions that do not code for proteins called NcRNAs (36), which can be classified as small non-coding RNAs (sncRNAs) and long non-coding RNAs (lncRNAs) depending on their length (<200 nucleotides and >200 nucleotides, respectively). Among them, the most studied NcRNAs are microRNAs (miRNAs, defined as single-stranded RNAs of approximately 22 nucleotides in length) (37), lncRNAs, circular RNAs (circRNAs, which as their name, they are not lineal RNAs, and arise from precursors mRNAs) (38,39), and PIWI interacting RNAs (piRNAs) (40).

The NcRNAs interact with many signaling pathways that involucrate cell metabolism, the lncRNA named cervical cancer DExH-box helicase 9 (DHX9) suppressive transcript (abbreviated as lncRNA CCDST) inhibits cell migration, invasion, anchorage-independent growth, and angiogenesis by the degradation of DHX9 protein, a member of DEAH-containing family of RNA helicases, which is responsible of many regulatory mechanisms in relation with cell growth. In CSCC, this lncRNA is downregulated in contrast with normal cervical squamous cells (41), LncRNA UICC is another epigenetic mechanism associated with International Federation of Gynecology and Obstetrics (FIGO) stage, lymph node metastasis and prognosis, however, it interacts via IL-6/STAT3 (42), lncRNA colon cancer associated transcript-1 (CCAT-1) (43), lncRNA DGCR5 interact via Wnt signaling pathway promoting tumor progression (44), and lncRNA CDKN2B-AS1 is upregulated in CC and its function is the regulation of cell proliferation (45). The metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) is another lncRNA, which high levels are associated with CC invasion and metastasis (46–48). Thymopoietin pseudogene 2 (TMPOP2), also named lncRNA-EBIC, was recently reported to highly expressed in CSCC, it interacts with EZH2 to downregulate the expression of E-cadherin (49).

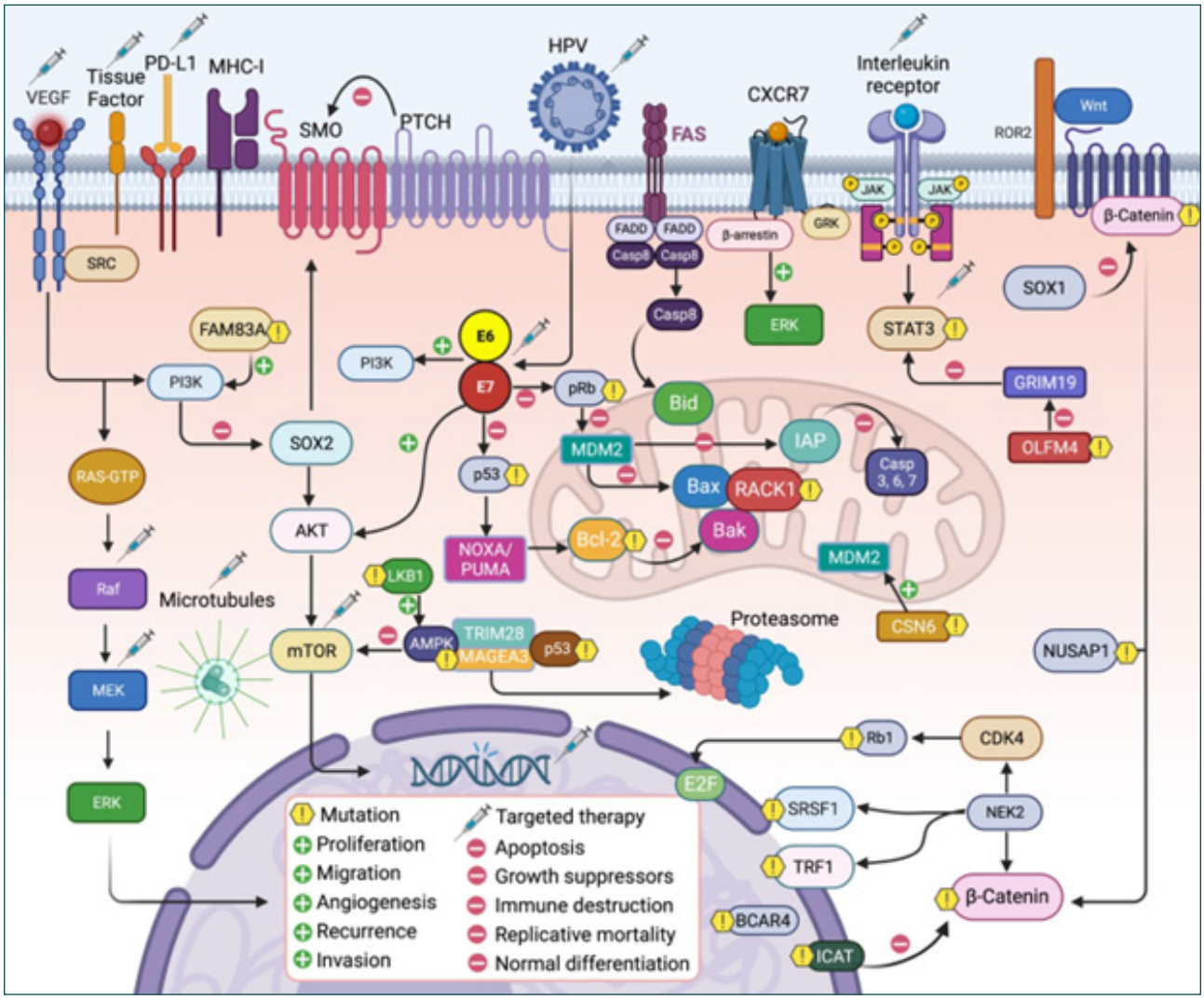

Figure 1. Regulation of the different signaling pathways associated with pathogenesis of cervical squamous cell carcinoma and its relationship with current targeted therapies. Created with Biorender.com

LncRNA in non-homologous end joining (NHEJ) pathway 1 (LINP1) is a lncRNA necessary in DNA repair activity by the interaction with Ku80 and DNA-PKcs, proteins of NHEJ pathway. LINP1 can be a potential therapeutic target and a possible radiotherapy-resistance biomarker (50), as lncRNA urothelial cancer associated 1 (UCA1) (51) and LINC00958 by miRNA-5095 regulates radio-resistance (52). Some lncRNAs interact with miRNAs, by increasing or decreasing its levels, as growth arrest special 5 (GAS5), which binds to miR-196a and miR-205 to downregulate its expression. GAS5 overexpression suppresses CSCC proliferation, and invasion (53,54), lncRNA NOC2L-4.1 is upregulated in CSCC, its function is the inhibition of miR-630/YAP1 pathway, which is associated with CC pathogenesis (55). LncRNA IDH1-AS1 regulates metabolic reprogramming to generate energy through increased glycolysis even in the presence of oxygen (Warburg effect) via c-Myc to collaborate with hypoxia inducible factor 1α (HIF1α) (56). Other lncRNAs such as PVT1 can determine chemoresistance by silencing miR-195 (57,58). The high expression of STXBP5-AS1, another lncRNA suppresses the proliferation and invasion by acting as a sponge of miR-96-5p to regulate PTEN expression (59), TP73-AS1 promotes proliferation and invasion via miR-329-3p/ARF1 (60), TUSC8 via

Table 1. Summary of the NcRNAs associated with progression and poor prognosis in metastatic cervical squamous cell carcinoma (mCSCC).

NcRNA	Targeted protein	Oncogenic processes	Tumor expression pattern	Reference
LncRNA CCDST	DHX9 protein DEAH-containing family of RNA helicases	Inhibits cell migration, invasion, anchorage-independent growth, and angiogenesis	Downregulation	(41)
LncRNA UICC	IL-6/STAT3 pathway	Lymph node metastasis and prognosis	Upregulation	(42)
LncRNA CCAT-1	MYC oncoprotein	Metastasis	Upregulation	(43)
LncRNA DGCR5	Wnt signaling pathway	Tumor progression	Upregulation	(44)
LncRNA CDKN2B-AS1	miR-181a-5p TGF-β1 signaling pathway	Regulation of cell proliferation	Upregulation	(45)
MALAT-1	miR-124, miR-145, miR-202-3p	Tumor invasion and metastasis	Upregulation	(46–48)
TMPOP2 (LncRNA-EBIC)	EZH2 E-cadherin	Metastasis	Upregulation	(49,80)
LINP1	Ku80 DNA-PKcs	Possible radiotherapy-resistance biomarker	Upregulation	(50)
LncRNA UCA1	CREB	Metastasis	Upregulation	(51)
LINC00958	miRNA-5095	Regulates radiotherapy resistance	Upregulation	(52)
GAS5	miR-196a miR-205	Tumor proliferation and Invasion	Downregulation	(53,54)
NOC2L-4.1	miR-630/YAP1 pathway	Proliferation and Invasion	Upregulation	(55)
IDH1-AS1	HIF1α	Warburg effect	Upregulation	(56)
PVT1	miR-195	Chemoresistance	Upregulation	(57,58)
STXBP5-AS1	miR-96-5p	Proliferation and Invasion	Downregulation	(59)
TP73-AS1	miR-329-3p/ARF1	Proliferation and Invasion	Upregulation	(60)
TUSC8	miR-641/PTEN	Cell growth	Downregulation	(61)
LncRNA XIST	miR-200a miR-200b	Tumor progression	Upregulation	(62,63)
LncRNA XLOC_006390	miR-331-3p miR-338-3p	Tumorigenesis and Metastasis	Upregulation	(64)
LncRNA-CTS	miR-505/ZEB260	Metastasis	Upregulation	(65)
LncRNA ATB/miR-144/ITGA6	SMAD/TGF signaling pathway	Proliferation and Invasion	Upregulation	(66)
LncRNA ANRIL	PI3K/AKT pathway	Carcinogenesis and Poor prognosis	Upregulation	(67)
CRNDE	PUMA	Cell growth	Downregulation	(68)
HOTAIR	STAT3 miR-148a HLA-G	Proliferation, Migration, Invasion, Worse prognosis, and Immunotherapy resistance	Upregulation	(69,70)
MEG3	P-STAT3	Cell growth, Apoptosis and Proliferation	Downregulation	(71)
LncRNA SPRY4-IT1	miR-101-3p/ZEB1	Poor prognosis, Migration, and Invasion	Upregulation	(72)
LncRNA TTN-AS1	miR-573/E2F3	Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(73)
LncRNA TUG1	miR-138-5p-SIRT1	Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(74)
lncRNA ZEB1-AS1		Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(75)

lncRNA LINC01535	miR-214/EZH2	Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(76)
lncRNA TP73	miRNA-607/cyclin D2	Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(77)
lncRNA SNHG12	miR-125b/STAT3	Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(78)
lncRNA ZNF667-AS1	miRNA-93-3p-dependent PEG3 downregulation	Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(79)
lncRNA XLOC_010588	c-Myc	Cell growth, Proliferation, Invasion, and Metastasis	Upregulation	(81)
miR-221-3p	THBS2	Proliferation, Invasion, Migration, and Angiogenesis	Upregulation	(82)
miR-21	RAS/MAPK signaling	Lymph node metastasis	Downregulation	(83)
miR-665	ERK/SMAD pathway TGFBR1	Cell cycle and drug resistance	Downregulation	(84)
miR-138-5p	LncRNA H19	FIGO stage, poor differentiation, lymph node metastasis, and poor overall survival	Downregulated	(85)
miR-106b	TGF-β-induced cell migration	Cell proliferation, migration, and invasion	Upregulation	(86)
miR-145	SMAD interacting protein 1 (SIP1)	Cell proliferation, migration, and invasion	Upregulation	(87)
miRNA-183		Cell invasion and metastasis	Downregulation	(88)
miR-218-5p	LYN/NF-κB signaling pathway	Cell growth and metastasis	Downregulation	(89)
miRNA-221-3p	THBS2	Metastasis	Upregulation	(90)
miR-29a	Methylation of tumor suppressor SOCS1	Invasion and metastasis	Downregulation	(91)
miR-124	amotL1	Vasculogenic mimicry, cell motility, endothelial migration, and cell polarity, and to regulate sprouting angiogenesis	Downregulation	(92)
miR-199b-5p	KLK10	Growth and metastasis	Upregulation	(93)
miR-519d	SMAD7 TGF-β signaling	Tumor progression and metastasis	Upregulation	(94)
miR-543	TRPM7	Tumor growth and metastasis	Downregulation	(95)
miRNA-21	TNFR1	lymph node metastasis	Upregulation	(96)
CircRNA-000284	miR-506	Cell proliferation, migration, and invasion	Upregulation	(97)
hsa_circ_0000745	E-cadherin	Cell proliferation, migration, and invasion	Downregulation	(98)

miR-641/PTEN (61), lncRNA XIST via Fus/miR-200a (62) and miR-200b (63), lncRNA XLOC_006390 facilitates CC tumorigenesis and metastasis through competing with miR-331-3p and miR-338-3p (64), lncRNA-CTS promotes metastasis by regulating miR-505/ZEB260 (65) and lncRNA ATB/miR-144/ITGA6 via SMAD/TGF signaling pathway (66). LncRNA ANRIL promotes carcinogenesis and poor prognosis in CSCC by the regulation of PI3K/AKT pathway (67).

As HPV proteins can interact with p53 expression, some lncRNAs such as CRNDE, interacts with p53 upregulated modulator of apoptosis (PUMA) protein,

which is necessary for cell growth (68). Homebox (HOX) transcript antisense RNA (HOTAIR) is another lncRNA that has been reported to be an important epigenetic mechanism in many types of cancers. HOTAIR upregulation is associated with proliferation, migration and invasion of CSCC, as observed in STAT3 inhibition (69), however, its function is not limited to this pathway, since it has been shown that HOTAIR interacts with miR-148a, which modulates the expression of human leukocyte antigen-G (HLA-G) associating worse prognosis and immunotherapy resistance (70). LncRNA MEG3 inhibits cell growth via ubiquitination and degradation of P-STAT3, in consequence, CC cells lead to apoptosis and the inhibition of proliferation (71). The lncRNA SPRY4-IT1 predicates poor prognosis and promotes tumor progression by regulating the miR-101-3p/ZEB1 which contributes to CC migration and invasion (72). LncRNA TTN-AS1 via miR-573/E2F3 (73), lncRNA TUG1 via miR-138-5p-SIRT1 (74), lncRNA ZEB1-AS1 (75), lncRNA LINC01535 via miR-214/EZH2 (76), lncRNA TP73 via miRNA-607/cyclin D2 (77), lncRNA SNHG12 via miR-125b/STAT3 (78), lncRNA ZNF667-AS1 via miRNA-93-3p-dependent PEG3 downregulation (79), lncRNA EBIC via EZH2 repressing E-cadherin (80), and lncRNA XLOC_010588 via c-Myc (81) promote cell growth, proliferation, invasion, and metastasis.

Exosomal miRNAs are involved in metabolic pathways as lncRNAs, miR-221-3p is highly expressed in CSCC and is associated with proliferation, invasion, migration and angiogenesis (82), miR-21 inactivation leads to overactivation of RAS/MAPK signaling, in consequence, the uncontrolled way leads to lymph node metastasis (83), miR-665 is downregulated in CC, its main function is the inactivation of ERK/SMAD pathway by regulating TGFBR1, its overexpression inhibits the cell cycle and drug resistance (84). Low levels of miR-138-5p are correlated with FIGO stage, poor differentiation, lymph node metastasis, and poor overall survival (OS) in CC patients (85). miR-106b is upregulated in CSCC, which is an epigenetic mechanism needed in transforming growth factor β (TGF-β) -induced cell migration (86), miR-145 modulates cell proliferation, migration and invasion by targeting SMAD interacting protein 1 (SIP1) (87), miRNA-183 is downregulated in CSCC, it acts as a tumor suppressor by inhibiting cell invasion and metastasis (88), miR-218-5p inhibits cell growth and metastasis via LYN/NF-κB signaling pathway (89), miRNA-221-3p directly targets THBS2, which is necessary for metastasis (90), miR-29a inhibits invasion and metastasis by modulating methylation of tumor suppressor SOCS1 (91), miR-124 represses vasculogenic mimicry and cell motility by targeting amotL1, which is a protein in charge to control endothelial migration and cell polarity, and to regulate sprouting angiogenesis (92), miR-199b-5p promotes growth and metastasis by downregulating KLK10, a tumor suppressor gene (93), miR-519d facilitates progression and metastasis by targeting SMAD7, which is necessary for the inactivation of TGF-β signaling (94), miR-543 is downregulated in CSCC, in consequence, it cannot target TRPM7, and leads to tumor growth and metastasis (95), and miRNA-21 promotes lymph node metastasis observed in an orthotopic xenograft mouse model (96). CircRNA-000284 (97) and hsa_circ_0000745 are circRNAs identified as epigenetic mechanisms in CSCC, they promote cell proliferation, migration, and invasion (98). All these epigenetic mechanisms are necessary to cervical cancer progression, and they are involucrate in many intracellular signaling pathways, as seen in Figure 2.

To understand the molecular mechanisms associated with poor prognosis and progression of CSCC, we decide to make a summary of those currently mechanisms. The importance to understand about theses mechanisms is to guide investigations that could give us new targeted therapies. Nowadays, there are new clinical trials involved in treat metastatic cervical cancer, mentioned in Table 2. (99–114)

Conclusion and discussion:

Cervical cancer is the fourth most common type of cancer in women worldwide and cervical squamous cell carcinoma (CSCC) is the most aggressive subtype of cervical cancers. This is why over time new research questions have arisen to better understand the CSCC physiopathogenesis and in this way, create new therapeutic strategies. Metastasis is observed in 15-30% in cervical cancer, informed by many authors, however, its prognosis is poorer. New targeted therapies schemes have been analyzed and along, however, despite this, the prognosis is still bleak, for that reason, new clinical trials have emerged and are currently being developed in order to obtain new treatment strategies.

This article seeks to analyze and to announce, through an exhaustive review of the literature, the epigenetic mechanisms associated with metastasis reported by various authors over time and its relationship with

poor prognosis of this type of cancer. The epigenetic mechanisms are closely related between each other's and with intracellular metabolic signaling pathways. Understanding the epigenetics in metastatic CSCC will allow health professionals to establish appropriate treatment and prognosis lines for this type of cancer according to its different molecular characteristics, with the aim of reducing mortality in women with metastatic CSCC and increasing the rate of survival.

Abbreviations:
AE: Adverse Effect
BCAR4: breast cancer anti-estrogen resistance 4
BIRC2/3: baculoviral IAP repeat containing 2/3
CC: cervical cancer.
CCAT-1: colon cancer associated transcript-1CCNA1: cyclin A1
CDKN2A: cyclin dependent kinase inhibitor 2A
CI: Confidence Interval
CircRNAs: circular RNAs
CSCC: cervical squamous cell carcinomas
DHX9: DExH-box helicase 9
DM: Diabetes Mellitus
DNMT1: DNA methyltransferase 1
EGFR: epidermal growth factor receptor
ELAVL2: ELAV like RNA binding protein 2
ERBB2: erb-b2 receptor tyrosine kinase 2
EZH2: enhancer of zeste homologue 2 gene
FAT1: FAT atypical cadherin 1
FIGO: International Federation of Gynecology and Obstetrics
GAS5: growth arrest special 5
GRB7: growth factor receptor bound protein 7
HIF1α: hypoxia inducible factor 1α
HIV: Human Immunodeficiency Virus
HOX: Homebox
HOTAIR: HOX transcript antisense RNA
HPV: Human Papillomavirus
HR: Hazzard Ratio
HSPB1: heat shock protein family B member 1
H3K27me3: trimethylation of lysine 27 on histone H3
KHSRP: KH-type splicing regulatory protein
KLF5: KLF transcription factor 5
LncRNAs: Long non-coding RNAs
MALAT-1: metastasis-associated lung adenocarcinoma transcript-1
mCSCC: metastatic Cervical Squamous Cell Cancer
MiRNAs: microRNAs
MYC: MYC proto-oncogene
NHEJ: non-homologous end joining
NcRNAs: non-coding RNAs
NOVA1: neuro-oncological ventral antigen 1
N/A: Not Applicable
OS: overall survival
PD-L1: programmed cell death 1 ligand
PD-L2: programmed cell death 2 ligand
PFS: Progression Free Survival
PiRNAs: PIWI interacting RNAs
PRC1: polycomb repressive complex 2
PRC2: polycomb repressive complex 1
PTBP1: polypyrimidine tract binding protein 1
PTEN: phosphate and tensin homolog
PUMA: p53 upregulated modulator of apoptosis
RBPs: RNA-binding proteins
RNASEH2A: ribonuclease H2A
SIP1: SMAD interacting protein 1
SMAD4: SMAD family member 4
SncRNAs: small non-coding RNAs
TGFBR2: transforming growth factor beta receptor 2
TERC: telomerase RNA component
TGF-β: transforming growth factor β
TMPOP2: thymopoietin pseudogene 2
TP63: tumor protein p63
UCA1: urothelial cancer associated 1

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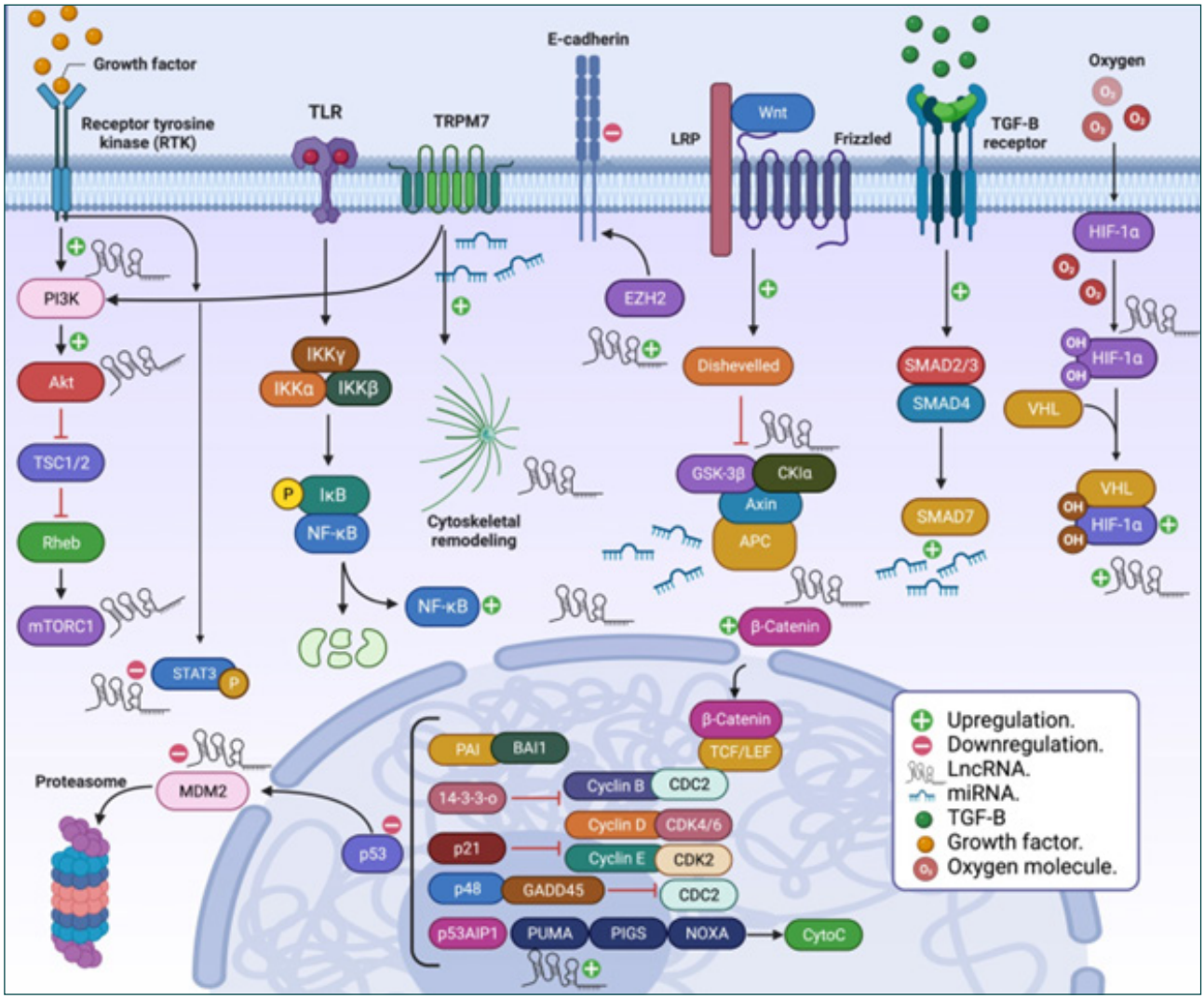

Figure 2. Non-coding RNAs and their signaling pathways regulation. Created with Biorender.com

Table 2. Resume of completed clinical trials and their results in metastatic Cervical Squamous Cell Cancer (mCSCC) in women of 18-64 years old, obtained by ClinicalTrials.gov

Clinical Trial	Phase	Allocation	Intervention Model	Study Start Date	Actual Study Completion Date	Experimental	Active Comparator	Median Progression Free Survival (PFS)	Median Overall Survival (OS)	Serious Adverse Effects	NCT Number	Ref
Phase II, Open-Label Study of Pazopanib or Lapatinib Monotherapy Compared With Pazopanib Plus Lapatinib Combination Therapy in Patients With Advanced and Recurrent Cervical Cancer	2	Randomized	Parallel Assignment	Nov, 2006	Jul, 2011	Pazopanib plus Lapatinib combination therapy	Lapatinib monotherapy and Pazopanib monotherapy	Combination therapy discontinued. Pazopanib (n=74) 18.1 weeks. Lapatinib (n=78) 17.1 weeks. HR (90% CI) 0.66 (0.48-0.91) p=0.013	Combination therapy discontinued. Pazopanib 50.7 weeks. Lapatinib 39.1 weeks. HR (90% CI) 0.67 (0.46-0.99) p=0.045	Any grade AE: Pazopanib 96% Lapatinib 92% Grade 3 AE: Pazopanib 11%, Lapatinib 13% Grade 4 AE: Pazopanib 12%, Lapatinib 9%.	NCT00430781	(99)
Efficacy and Safety Study of First-line Treatment With Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Women With Persistent, Recurrent, or Metastatic Cervical Cancer (MK-3475-826/ KEYNOTE-826)	3	Randomized	Parallel Assignment	Oct, 2018	Estimated: Jun, 2024	Pembrolizumab plus Chemotherapy (Paclitaxel, cisplatin, carboplatin, and bevacizumab)	Placebo plus Chemotherapy (Paclitaxel, cisplatin, carboplatin, and bevacizumab)	Pembrolizumab group 10.4 months, HR 0.58 (95% CI, 0.44-0.77) p<0.001	Pembrolizumab group 24 months, HR 0.61 (95% CI, 0.44-0.84) p=0.001	Any grade AE: Pembrolizumab group 99.3% Placebo group 99.4% Grade 3-5 AE: Pembrolizumab group 81.8% Placebo group 75.1%	NCT03635567	(100)
Phase II study of atezolizumab in combination with bevacizumab in patients with advanced cervical cancer	2	N/A	Single Group Assignment	March, 2017	Jan, 2021	Atezolizumab plus Bevacizumab combination therapy	N/A	Combination therapy 2.9 months (95% CI, 1.8-6).	Combination therapy 8.9 months (95% CI, 3.4-21.9)	Any grade AE: 100% Serious EA: 0%	NCT02921269	(101)
Paclitaxel plus oxaliplatin for recurrent or metastatic cervical cancer: a New York Cancer Consortium Study	2	N/A	Single Group Assignment	Jan, 2003	March, 2010	Oxaliplatin plus Paclitaxel	N/A	Combination therapy (Total of 135 cycles) 21 weeks (95% CI, 14.7-27.2)	Combination therapy (Total of 135 cycles) 52 weeks (95% CI, 39.4-64.8)	Any grade AE: 100% Serious AE: 100%	NCT00057863	(102)
Phase II Evaluation of Nivolumab in the Treatment of Persistent or Recurrent Cervical Cancer (NCT02257528/NRG-GY002)	2	N/A	Single Group Assignment	May, 2015	March, 2019	Nivolumab	N/A	Nivolumab 3.5 months (90% CI, 1.9-5.1)	Nivolumab 14.5 months (90% CI, 8.3-26.8)	Any grade AE: 96% Serious AE: 48%	NCT02257528	(103)

Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study	2	N/A	Single Group Assignment	June, 2018	Aug, 2022	Tisotumab vedotin	N/A	Tisotumab vedotin 4.2 months (95% CI, 3-4.4)	Tisotumab vedotin 12.1 months (95% CI, 9.6-13.9)	Any grade AE: 98.02% Serious AE: 43.56%	NCT03438396	(104)
Continued.												
EMPOWER CERVICAL-1: Effects of cemiplimab versus chemotherapy on patient-reported quality of life, functioning and symptoms among women with recurrent cervical cancer	3	Randomized	Parallel assignment	Sept, 2017	Apr, 2023	Cemiplimab	Topotecan or irinotecan, gemcitabine, vinorelbine plus pemetrexed	Cemiplimab group 2.8 months (95% CI, 2.6-3.9) Chemotherapy group 2.9 months (95% CI, 2.7-3.4) HR for disease progression or death 0.75 (95% CI, 0.63-0.89) p<0.001	Cemiplimab group 12 months (95% CI, 10.3-13.5) Chemotherapy group 8.5 months (95% CI, 7.5-9.6)	Any grade AE: Cemiplimab group 87.67% Chemotherapy group 91.03% Serious AE: Cemiplimab group 30.33% Chemotherapy group 27.93%	NCT03257267	(105, 106)
Basket Study to Evaluate the Therapeutic Activity of Simlukafusp Alfa as a Combination Therapy in Participants With Advanced and/or Metastatic Solid Tumors	2	Non-Randomized	Parallel assignment	Feb, 2018	Dec, 2021	Simlukafusp alfa plus atezolizumab	N/A	Cohort J (n=44): 3.7 months (95% CI, 3.3-9) Cohort N (n=1): 1.9 months (95% CI, N/A to N/A)	Cohort J (n=44): N/A Cohort N (n=1): N/A	Any grade AE: Cohort J: 100% Cohort N: 100% Serious AE: Cohort J: 68.09% Cohort N: 100%	NCT03386721	(107)
Clinical Trial of PM00104 (Zalypsis®) in Patients With Advanced and/or Metastatic Endometrial or Cervical Cancer Previously Treated With One Line of Systemic Chemotherapy	2	N/A	Single Group Assignment	Aug, 2009	Sept, 2011	Zalypsis (PM00104)	N/A	Zalypsis 1.5 months (95% CI, 1.5-1.8)	Zalypsis 5.6 months (95% CI, N/A – N/A)	Any grade AE: 100% Serious AE: 42.86%	NCT00900562	(108)
Ipilimumab in Treating Patients With Metastatic or Recurrent Human Papilloma Virus-Related Cervical Cancer	2	N/A	Single Group Assignment	Dec, 2012	Nov, 2021	Ipilimumab	N/A	Ipilimumab 2.5 months (95% CI, 2-3.2)	Not mentioned	Any grade AE: 100% Serious AE: 59.52%	NCT01693783	(109)

A phase I/II study of extended field radiation therapy with concomitant paclitaxel and cisplatin chemotherapy in patients with cervical carcinoma metastatic to the para-aortic lymph nodes: a Gynecologic Oncology Group study	1	N/A	Single Group Assignment	Nov, 1999	Jul, 2009	Cisplatin, paclitaxel, brachytherapy plus radiation therapy	N/A	Probability of Disease-Free Survival at 2 years 0.65 (95% CI, 0.44-0.86)	Probability of Overall Survival at 2 years 0.80 (95% CI, 0.62-0.97)	Any grade AE: Arm 1, 2 and 3 P I: 100% Arm 4 P I: 66.67% Arm 2 P II: 88.24% Serious AE: Arm 3, P I: 33.33% Arm 4, P I: 66.67% Arm 2, P II: 5.88%	NCT00003377	(110)
Complete Regression of Metastatic Cervical Cancer After Treatment With Human Papillomavirus–Targeted Tumor-Infiltrating T Cells	2	Non-Randomized	Parallel Assignment	Apr, 2012	Aug, 2016	Fludarabine, cyclophosphamide, Young TIL plus aldesleukin	N/A	Overall number of participants: 18 Partial response: 3 (16.7%) Complete response: 2 (11.1%) Progressive disease: 12 (66.7%) Stable disease: 1 (5.6%)		Any grade AE: 94.44% Serious AE: 22.22%	NCT01585428	(111)
Continued												
Efficacy and Safety of Sintilimab Plus Anlotinib for PD-L1–Positive Recurrent or Metastatic Cervical Cancer: A Multicenter, Single-Arm, Prospective Phase II Trial	2	Non-Randomized	Single Group Assignment	Dec, 2019	Dec, 2022	Sintilimab plus anlotinib	N/A	Median PFS 9.4 months (95% CI, 8-14.6) 6-month PFS 73.1% (95% CI, 60.1-88.9%)	OS events occurred in 10 patients (23.8%). Median OS was not reached. 12-month OS rate was 73.8% (95% CI, 59.3-91.7%)	Any grade AE: 85.8% Serious AE: 16.7%	Not mentioned	(112)
Sunitinib Malate in Treating Patients With Uterine Cervical Cancer That is Stage IVB, Recurrent, or Cannot Be Removed By Surgery	2	N/A	Single Group Assignment	Jan, 2007	Marc, 2009	Sunitinib malate	N/A	Objective Response Rate (n=19): 0 (95% CI, 0.1-7.6)		Any grade AE: 100% Serious AE:73.68%	NCT00389974	(113)
Temsirolimus in Treating Patients With Cervical Cancer That Is Recurrent, Locally Advanced, Metastatic, or Cannot Be Removed By Surgery	2	N/A	Single Group Assignment	Dec, 2009	Nov, 2012	Temsirolimus	N/A	Objective Response Rate (n=33): 3 (95% CI, 0.1-15.8)		Any grade AE: 100% Serious AE: 40.54%	NCT01026792	(114)

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