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Long non-coding RNAs and chemotherapy resistance in cervical cancer

RNAs longos não codificantes e resistência quimioterápica em câncer cervical

ARN largos no codificantes y resistencia a la quimioterapia en el cáncer cervical

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ABSTRACT

Objective: To identify lncRNAs associated with chemotherapy resistance in cervical cancer (CC). **Methods:** This study is a systematic literature review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42023432017. Searches were performed in databases such as PubMed, ScienceDirect, and Web of Science, resulting in the selection of 21 articles published between 2017 and 2023. **Results:** The findings highlighted that 19 lncRNAs are implicated in resistance to four chemotherapeutic agents, including GAS5, which was the target of the greatest number of studies. These lncRNAs are involved in resistance to paclitaxel (PTX), 5-fluorouracil (5-FU), and doxorubicin (DTX). **Final considerations:** These results underscore the importance of lncRNAs as potential markers of treatment response and suggest that miRNA-mediated regulation may directly influence biological pathways that are frequently dysregulated in cancer.[1]

Keywords: Chemotherapy, lncRNA, Prognosis, Resistance, GAS5.

RESUMO

Objetivo: Identificar lncRNAs associados à resistência à quimioterapia no câncer cervical (CC). **Métodos:** O estudo é uma revisão sistemática de literatura conduzida de acordo com as diretrizes do *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), o protocolo foi previamente registrado no International Prospective Register of Systematic Reviews (PROSPERO) sob o código CRD42023432017 com buscas realizadas em bases de dados como PubMed, ScienceDirect e Web of Science, resultando na seleção de 21 artigos publicados entre 2017 e 2023. **Resultados:** Os achados destacaram que 19 lncRNAs estão implicados na resistência a quatro agentes quimioterápicos, incluindo o GAS5, que foi o alvo de um maior número de estudos. Esses lncRNAs estão envolvidos na resistência ao paclitaxel (PTX), ao 5-fluorouracil (5-

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FU) e à doxorrubicina (DTX). **Considerações finais:** Esses resultados ressaltam a importância dos lncRNAs como potenciais marcadores de resposta ao tratamento e sugerem que a regulação por miRNAs pode influenciar diretamente vias biológicas frequentemente desreguladas no câncer.

Palavras-chave: Quimioterapia, lncRNA, Prognóstico, Resistência, GAS5.

RESUMEN

Objetivo: Identificar lncRNAs asociados con la resistencia a la quimioterapia en el cáncer cervical (CC). **Métodos:** Este estudio es una revisión sistemática de la literatura realizada de acuerdo con las directrices del Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). El protocolo fue previamente registrado en el International Prospective Register of Systematic Reviews (PROSPERO) bajo el código CRD42023432017. Las búsquedas se realizaron en bases de datos como PubMed, ScienceDirect y Web of Science, lo que resultó en la selección de 21 artículos publicados entre 2017 y 2023. **Resultados:** Los hallazgos destacaron que 19 lncRNAs están implicados en la resistencia a cuatro agentes quimioterapéuticos, incluido GAS5, que fue el objetivo del mayor número de estudios. Estos lncRNAs están involucrados en la resistencia al paclitaxel (PTX), al 5-fluorouracilo (5-FU) y a la doxorrubicina (DTX). **Consideraciones finales:** Estos resultados resaltan la importancia de los lncRNAs como posibles marcadores de respuesta al tratamiento y sugieren que la regulación mediada por miRNAs puede influir diretamente en vías biológicas que se encuentran frecuentemente desreguladas en el cáncer.

Palabras clave: Quimioterapia, lncRNA, Pronóstico, Resistencia, GAS5.

INTRODUCTION

Cervical cancer (CC) is the fourth most common malignancy among women and remains a major global public health challenge. It is estimated that by 2030, both incidence and mortality will increase from 400,000 to 700,000 annual cases (BRAY F, et al., 2018). In Brazil, CC ranks as the third most frequent cancer among women, with an estimated 17,010 new cases projected for the 2023–2025 triennium (INCA, 2023).

The etiology of CC is strongly associated with persistent infection by the Human Papillomavirus (HPV), which is responsible for approximately 99% of cases. Among the viral subtypes, HPV-16 and HPV-18 account for about 70% of precursor lesions and invasive tumors (OPS, 2025). Additionally, factors such as early onset of sexual activity, multiple sexual partners, smoking, HIV coinfection, and prolonged use of oral contraceptives further increase the risk of disease development (JOHNSON C, et al., 2019).

Treatment strategies include surgery, radiotherapy, and chemotherapy, depending on tumor stage and patient clinical condition (CHEN W, et al., 2023). In advanced cases, concurrent chemoradiotherapy is commonly employed to improve therapeutic outcomes (FANG X, et al., 2020). However, chemoresistance remains one of the major challenges, as tumor cells can activate adaptive mechanisms such as alterations in drug transport, modification of molecular targets, and epigenetic changes, ultimately reducing drug efficacy and worsening prognosis (LIU S, et al., 2021).

Several mechanisms contribute to resistance to chemotherapeutic agents. One of the most relevant involves ATP-binding cassette (ABC) transporters, which act as efflux pumps through ATP hydrolysis, decreasing intracellular drug accumulation (GIDDINGS E, et al., 2021). In CC, chemotherapeutic agents such as cisplatin may induce epithelial–mesenchymal transition (EMT), a process associated with increased invasiveness and resistance. Transcription factors involved in EMT also contribute to chemoresistance, including SNAIL1, which enhances cell survival under high cisplatin exposure, and iASPP, whose overexpression reduces cisplatin-induced apoptosis (BHATTACHARJEE R, et al., 2022).

In this context, long non-coding RNAs (lncRNAs) have emerged as critical regulators of tumor biology. These RNA molecules, longer than 200 nucleotides, do not encode proteins but play essential roles in gene

expression regulation at multiple levels (HE J, et al., 2020). lncRNAs interact with DNA, RNA, and proteins, influencing transcription, translation, and mRNA stability. Furthermore, they act as competing endogenous RNAs (ceRNAs), functioning as miRNA sponges and modulating signaling pathways involved in proliferation, invasion, metastasis, apoptosis, and drug resistance (SAW P, et al., 2021; LIU M, et al., 2018).

The involvement of lncRNAs in CC progression has been demonstrated in several molecular pathways. For instance, the NNT-AS1/miR-186/HMGB1 axis contributes to reduced cell death when dysregulated (MODABBER N, et al., 2023). Similarly, the lncRNA NEAT1 is overexpressed in CC and functions as a ceRNA for miR-133a, leading to increased expression of the transcription factor SOX4 and inhibition of apoptosis (YUAN L, et al., 2019). Additionally, lncRNAs such as HNF1A-AS1 promote tumor progression by sponging miR-34b, resulting in the upregulation of TUFT1 and enhanced cell cycle progression (LUO X, et al., 2019).

Despite growing evidence supporting the role of lncRNAs in chemoresistance, current knowledge remains fragmented and lacks systematic integration. Therefore, this study aims to comprehensively map lncRNAs associated with chemotherapy resistance in cervical cancer.

METHODS

Study characterization

This study is a systematic literature review conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (PAGE M, et al., 2021). The protocol was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42023432017.

The central question of this investigation was: “What is the role of lncRNAs in chemoresistance in cervical cancer (CC)?” To formulate this question, the PICOS strategy (Methley A, et al., 2014) was applied, detailed as follows:

Population (P): Cell lines derived from cervical cancer.

Intervention (I): lncRNAs with altered expression levels.

Comparison (C): Evaluation of differential expression of lncRNAs in relation to drug resistance.

Outcome (O): Identification of lncRNAs involved in chemoresistance.

Study Design (S): Experimental investigations.

Eligibility criteria

Only articles that met the following criteria were included: (1) written in English; (2) published between 2017 and 2023; and (3) studies using cervical cancer cell lines that addressed the relationship between lncRNAs and chemoresistance factors. In addition, only experimental studies that presented clear methodological descriptions and evaluated outcomes related to drug resistance, such as cell proliferation, apoptosis, migration, invasion, or response to chemotherapeutic agents, were considered eligible for inclusion.

The exclusion criteria were: (1) abstracts, reports, review articles, monographs, and dissertations; (2) in silico studies without experimental validation; and (3) studies that did not directly investigate the role of lncRNAs in chemoresistance or that did not present sufficient data for analysis. Studies that focused exclusively on secondary databases or that did not present a clear association between lncRNA expression and drug response were also excluded, ensuring greater consistency and relevance of the selected studies.

Data sources and search strategies

Searches were conducted in the following electronic databases: U.S. National Library of Medicine (PubMed), ScienceDirect, and Web of Science. The search strategy was developed using combinations of controlled descriptors and keywords related to long non-coding RNAs, cervical cancer, and chemoresistance, combined with Boolean operators (AND, OR). Filters were applied to restrict results to articles published between 2017 and 2023 and written in English.

The search strings were adapted for each database as follows:

PubMed = (("lncRNA" OR "long non coding RNA" OR "long non-coding RNA") AND ("cervical cancer" OR "cervical carcinoma") AND ("drug resistance" OR "chemoresistance" OR "cisplatin" OR "paclitaxel" OR "doxorubicin" OR "5-fluorouracil")) Filters: 2017–2023; English; experimental studies. ScienceDirect = ("lncRNA" OR "long non coding RNA") AND ("cervical cancer") AND ("drug resistance" OR "chemotherapy resistance" OR "cisplatin" OR "paclitaxel" OR "doxorubicin" OR "5-fluorouracil") Filters: Research articles; English; 2017–2023. Web of Science = (("lncRNA" OR "long non coding RNA") AND ("cervical cancer" OR "cervical carcinoma") AND ("chemoresistance" OR "drug resistance" OR "cisplatin" OR "paclitaxel" OR "doxorubicin" OR "5-fluorouracil")).

Study selection

The reference management software Zotero version 6.0 was used to identify and remove duplicate records and to assist in the screening process according to the predefined eligibility criteria. After the final selection of the studies, data extraction was performed, and the information was organized using Microsoft Excel 2019. The following characteristics were extracted from each included study: evaluated lncRNA, expression pattern (upregulation or downregulation), biological function, corresponding chemotherapeutic drug, target genes and signaling pathways involved, and study reference.

Methodological quality assessment of the included studies

After applying the eligibility criteria, the methodological quality of the included studies was evaluated independently by the reviewers using the Joanna Briggs Institute Critical Appraisal Tools (JBI) (https://jbi-global wiki.refined.site/space/MANUAL/355829259/8.3+The+JBI+approach+to+mixed+method+systematic+reviews). The checklist for quasi-experimental studies was selected because the included articles consisted predominantly of experimental investigations using cervical cancer cell lines, without randomization or clinical intervention, which characterizes a quasi-experimental design. The JBI checklist evaluates methodological rigor through specific criteria related to study design, measurement reliability, outcome assessment, and statistical analysis. Each item was classified as Yes, No, Unclear, or Not applicable.

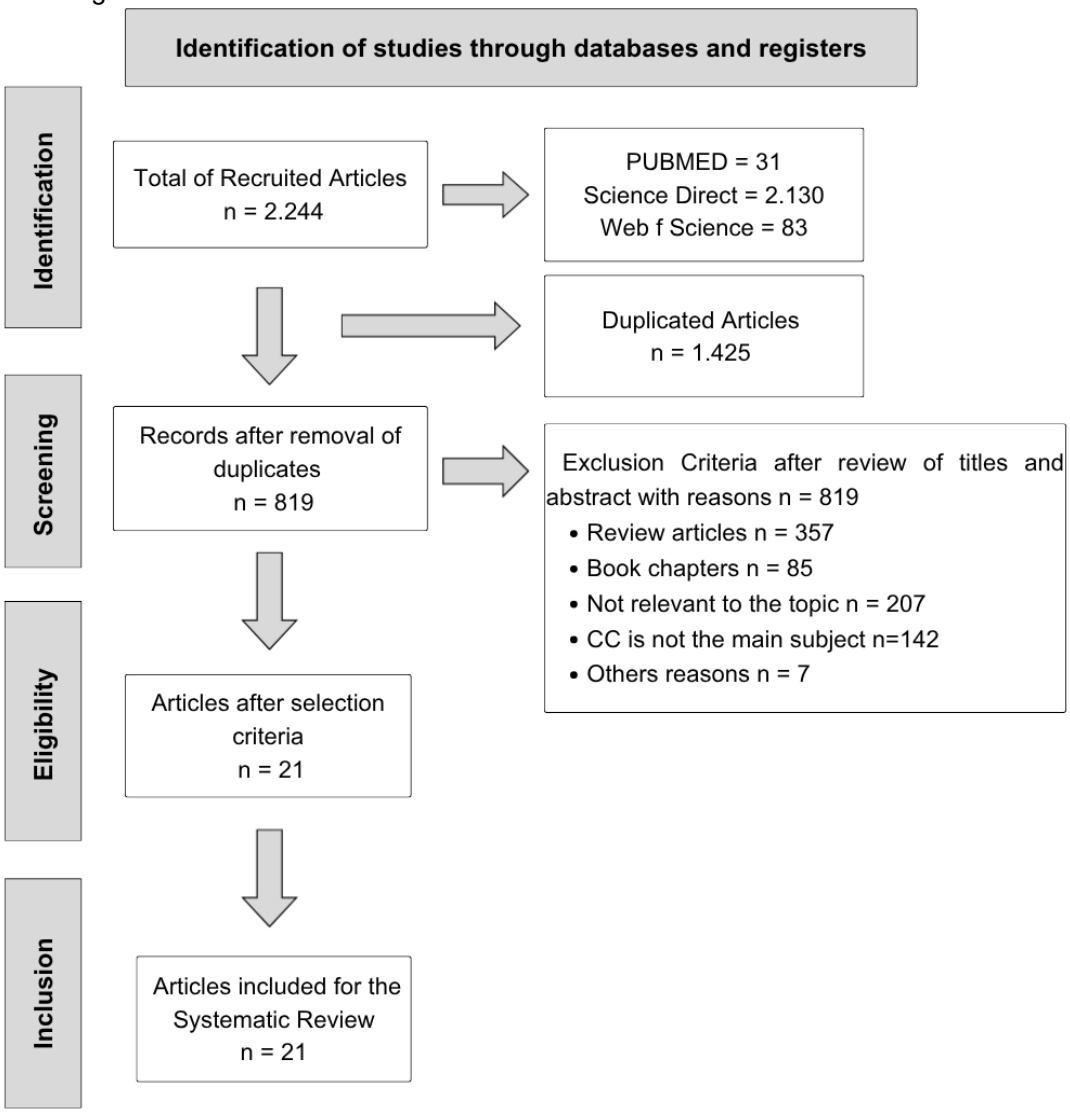
To estimate the risk of bias, scores were assigned according to the number of positive responses, as follows: 1 to 4 points (high risk of bias); 5 to 6 points (moderate risk of bias); 7 points or more (low risk of bias). The quality assessment was performed independently by two reviewers, and disagreements were resolved by consensus. The methodological quality scores were used to describe the overall reliability of the included studies; however, no study was excluded based on quality assessment, and all selected articles were included in the qualitative synthesis due to the limited number of available experimental studies on this topic.

RESULTS

Characterization of the included studies

A total of 2,244 studies were identified across the selected databases, following PRISMA guidelines. After removing duplicate records (n = 1,425), 819 articles remained for the screening stage. During the title and abstract review, 798 studies were excluded for not meeting the established inclusion criteria. Ultimately, 21 articles met all eligibility criteria and were included in the systematic review, as shown in the study selection flowchart (**Figure 1**).

Figure 1 - PRISMA Flowchart of articles located during the Systematic Review of CC according to the databases.



Source: Sousa LR, et al., 2026.

Bias Analysis

Table 1 presents the assessment of the methodological quality of the included studies, carried out using the Joanna Briggs Institute Critical Appraisal Tools (JBI) through the Checklist for Quasi-Experimental Studies. Eight articles scored 7 (low risk of bias), while thirteen showed scores of 5 or 6 (moderate risk of bias). Each row represents a specific study, and the columns contain information regarding various evaluation criteria.

Table 1 - Quality assessment of the methods used in the included studies conducted using the Joanna Briggs Institute Critical Appraisal Tools (JBI).

Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total (Yes)	Trend Level
TIAN et al., (2022)	**Y	Y	*N	Y	***NA	Y	Y	Y	Y	7	Low
WANG et al., (2017)	Y	Y	N	Y	N	Y	N	Y	Y	6	Moderate
FENG et al., (2019)	Y	Y	N	Y	N	N	Y	Y	Y	7	Low
YAO et al., (2019)	Y	Y	N	NA	N	N	Y	Y	Y	5	Moderate
SHAO et al., (2021)	NA	Y	N	Y	Y	Y	N	Y	Y	6	Moderate
MAO et al., (2019)	Y	NA	N	Y	N	Y	N	Y	Y	5	Moderate
TIAN et al., (2022)	Y	Y	N	Y	N	Y	Y	NA	Y	6	Moderate
Zhang et al., (2022)	Y	Y	NA	NA	N	Y	Y	Y	Y	6	Moderate
DU et al., (2022)	Y	Y	N	Y	N	NA	N	Y	Y	5	Moderate
LIU et al., (2020)	Y	Y	N	Y	Y	N	N	Y	Y	6	Moderate
HOU et al., (2020)	Y	Y	N	Y	N	Y	Y	Y	Y	7	Low
MA et al., (2020)	Y	Y	N	Y	N	Y	Y	Y	Y	7	Low
SHEN et al., (2017)	Y	Y	N	Y	N	Y	Y	Y	Y	7	Low
YANG et al., (2022)	Y	Y	N	Y	N	Y	NA	Y	Y	6	Moderate
CAI et al., (2019)	Y	NA	N	Y	N	Y	Y	Y	Y	6	Moderate
SUN et al., (2023)	Y	Y	N	Y	N	Y	Y	Y	Y	7	Low
WEN et al., (2017)	Y	Y	NA	Y	N	Y	Y	Y	Y	7	Low
WEI et al., (2019)	Y	Y	N	Y	N	Y	Y	Y	Y	7	Low
FANG et al., (2020)	Y	Y	N	Y	N	Y	N	Y	Y	6	Moderate
CHI et al., (2023)	Y	NA	N	NA	N	Y	Y	Y	Y	5	Moderate
HE et al., (2022)	Y	Y	N	Y	N	Y	N	Y	N	5	Moderate

*Y = Yes; **N = No; ***NA = Not Applicable.
Source: Sousa LR, et al., 2026.

LncRNAs Involved in Chemotherapeutic Resistance

The analysis of the studies identified 19 lncRNAs associated with chemoresistance in CC. Cisplatin (DDP) was the most frequently evaluated drug, with 15 lncRNAs implicated. The lncRNA GAS5, which was downregulated, was the most extensively investigated and was consistently associated with DDP resistance. The lncRNA HOTAIR stood out for being involved in resistance to three different chemotherapeutic agents (DDP, PTX, and DTX). In contrast, only one lncRNA (NEAT1) was related to 5-FU.

In general, most lncRNAs showed increased expression (n=16), which was associated with phenotypes of proliferation, invasion, metastasis, and epithelial–mesenchymal transition, while only three exhibited downregulation (**Table 2**).

Table 2 - Presents the analyzed lncRNAs, their expression profiles, associated biological functions, corresponding chemotherapeutic agents, and the miRNAs or pathways targeted by these molecules.

LncRNAs	Expression	Biological Function	Corresponding Drugs	Targets or Pathways	Reference
SPRY4-IT1	↑*	Migration, Invasion, Proliferation, Metastasis, Apoptosis suppression	DDP	-	CAI; DENG, 2019
PDHB-AS	↓*	Migration, Invasion, Proliferation, Metastasis, Apoptosis suppression	DDP	miR-4536-5p	CHI et al., 2023
OTUD6B-AS1	↑	Cellular proliferation, Cellular migration and invasion, Apoptosis	DDP	miR-206	HOU et al., 2022
GAS5	↓	Cellular proliferation, invasion, and migration	DDP	miR-21	WEN et al., 2017
GAS5	↓	Cellular proliferation, invasion, and migration, TEM	DDP	miR-21	FANG et al., 2020
GAS5	↓	Cellular proliferation, Cellular migration and invasion, Apoptosis	DDP	miR-21	YAO et al., 2019
NEAT1	↑	Promotes cancer cell proliferation and inhibits apoptosis	5-Fu	miR-34a	SHAO et al., 2021
LINC00958	↑	Cellular proliferation, invasion, and migration, TEM	DDP	miR-185-5p	TIAN et al., 2022
LINC00511	↑	Cellular proliferation, migration, and invasion, apoptosis	PTX	-	MAO et al., 2019
PVT1	↑	Cellular proliferation, invasion, and migration	PTX	miR-195	SHEN et al., 2017
ZFAS1	↑	Cellular proliferation, migration, and invasion, apoptosis	DDP	-	FENG et al., 2019
ANXA2P2	↑	Proliferation, invasion, and migration of cells	DDP	miR-361-3p	HE et al., 2022
NNT-AS1	↑	Proliferation, invasion, and migration of cells	DDP	miR-186	LIU et al., 2022
PCAT6	↑	Proliferation, invasion, and migration of cells	DDP	miR-543	MA et al., 2020
BCYRN1	↑	Proliferation, invasion, and migration of cells	DDP	miR-330-5p	SUN et al., 2022
SOX21-AS1	↑	Proliferation, invasion, and migration of cells	DDP	miR-9-3p	TIAN et al., 2022
UCA1	↑	Promotes the proliferation of cancer cells and inhibits apoptosis	DDP	-	WANG et al., 2017
TUG1	↑	Proliferation, invasion, and migration of cells	DDP	-	WEI et al., 2019
SNHG15	↑	Proliferation, invasion, and migration of cells	DDP	miR-4735-3p	YANG et al., 2022
HOTAIR	↑	Proliferation, invasion, and migration of cells, TEM	DDP, PTX e DTX	miR-29b	ZHANG et al., 2022

Nota: LncRNAs: expression, biological function, chemotherapeutics, and targets in Cervical Cancer↑* = Positive regulation of expression; ↓* = Negative regulation of expression.
Source: Sousa LR, et al., 2026.

DISCUSSION

Chemotherapy remains the main therapeutic option for patients with CC in advanced stages or for those who are not eligible for surgical treatment (ZHANG L, et al., 2021). However, the emergence of chemoresistance represents one of the greatest clinical challenges, resulting in poor prognosis, tumor recurrence, and an increased risk of metastasis (FANG X, et al., 2020). This phenomenon arises from multiple cellular mechanisms, including the activation of survival signaling pathways, increased drug efflux by membrane transporters, and alterations in the cell cycle, which collectively reduce the effectiveness of antineoplastic agents (LIU S, et al., 2022; FENG L, et al., 2019).

In this context, lncRNAs emerge as central elements in modulating the chemotherapeutic response, as they participate in physiological and pathological processes critical to cellular homeostasis and tumorigenesis (HE S, et al., 2021). In this review, 19 differentially expressed lncRNAs were identified in cervical cancer, with emphasis on MEG3, which was downregulated and associated with resistance to cisplatin (DDP). This drug, widely used in cancer treatment, acts by binding to the purine bases of DNA, forming intra- and interstrand adducts and inducing cellular apoptosis (GHOSH S, 2019; MARKMAN M, 2014).

Among the findings, 15 lncRNAs were related to DDP resistance. Among them, GAS5 was consistently described as being downregulated, resulting in the overexpression of miR-21 and consequent inhibition of the tumor suppressor gene *PDCD4,* a mechanism associated with a resistant phenotype (CHEN W, et al., 2023, YAO T, et al., 2019). Interestingly, Wen Q, et al. (2017) observed that the overexpression of GAS5, concomitant with the reduction of miR-21 levels, restored cell sensitivity to cisplatin, suggesting a potential GAS5/miR-21/PDCD4 regulatory axis as a therapeutic target.

Furthermore, the lncRNA ANXA2P2 has been described as a potential regulator of miR-361-3p, although its molecular functions are not yet fully elucidated (FANG X, et al., 2020). Additional evidence, such as that reported by Qu S, et al. (2021), indicates that this miRNA may play a relevant role in the expansion of tumor-initiating cells and in chemoresistance in other contexts, reinforcing the need for functional studies in cervical cancer.

In addition to the lncRNAs associated with cisplatin resistance, those related to paclitaxel (PTX) resistance were also identified. This chemotherapeutic agent exerts its activity by interfering with microtubule dynamics, structures that are essential for cell division (FANG X, et al., 2020). By inhibiting depolymerization, PTX promotes structural instability, leading to cell cycle arrest and, consequently, apoptosis of tumor cells (BRANDÃO HN, et al., 2010).

Among the lncRNAs that may be implicated in reducing drug sensitivity is LINC00511, which has been described as upregulated in cervical cancer cells, being associated with poor prognosis and increased chemoresistance. Silencing of this lncRNA not only inhibits cell proliferation but also restores sensitivity to PTX, suggesting its potential as a therapeutic target (MAO B, et al., 2019). Similarly, the lncRNA PVT1 has been associated with PTX resistance through the epigenetic silencing of miR-195, a mechanism that contributes to maintaining the resistant phenotype (SHEN C, et al., 2017).

Regarding 5-fluorouracil (5-FU), only the lncRNA NEAT1 was consistently associated with resistance in cervical cancer. 5-FU acts as an antimetabolite, interfering with nucleic acid synthesis and impairing both replication and protein synthesis, resulting in inhibited cell growth (SETHY C e KUNDU C, 2021). Although widely used in the treatment of various neoplasms, including cervical cancer (WEN Q, et al., 2017), its effectiveness may be limited by the development of adaptive resistance mechanisms.

In this context, Shao X, et al. (2021) demonstrated that NEAT1 overexpression is correlated with 5-FU resistance, a phenomenon linked to the increased dependence of tumor cells on aerobic glycolysis, known as the Warburg effect (PAVLOVA N e THOMPSON C, 2016). This observation reinforces the hypothesis that modulation of metabolic pathways mediated by lncRNAs may play a crucial role in chemoresistance.

The lncRNA HOTAIR, in turn, was the only one associated with resistance to DDP, PTX, and DTX. DTX is a chemotherapeutic drug that acts similarly to PTX, interfering with the cell cycle and inhibiting cancer cell

growth (ZHOU C, et al., 2023). Overexpression of HOTAIR induces migration, proliferation, and facilitates epithelial–mesenchymal transition (EMT) in neoplastic cells, promoting chemoresistance through the miR-29b/PTEN/PI3K signaling pathway (ZHANG W, et al., 2022).

The lncRNAs discussed in this study show great potential as novel targets for diagnosis, prognosis, and targeted therapies. A notable example is MEG3, which showed an association with lower survival rates in patients with low expression levels in a case-control study (WAN S e ZHAO H, 2020). Similarly, GAS5, which exhibited higher resistance to DDP, was associated with a worse prognosis in patients with low expression levels (CAO S, et al., 2014).

HOTAIR, which showed greater resistance to chemotherapeutic agents, is widely explored as a potential diagnostic biomarker due to its high sensitivity and specificity. In one study (LIU M e LI N, 2023), this RNA demonstrated high accuracy rates of 92.7% and 89.3% in serum and vaginal discharge samples, respectively.

NEAT1 plays different roles in various cancers and is considered a potential biomarker and therapeutic target in breast and gynecological cancers (cervical, endometrial, ovarian, and vulvar). In contrast, in gastric and lung cancers, it is associated with poor prognostic factors, including chemoresistance (FARZANEH M, et al., 2023; ZHANG Y e WEN Y, 2023; SWEEF O, et al., 2024).

Thus, the molecular mechanisms associated with cervical cancer need to be better elucidated to enable advances in diagnosis, treatment, and prognosis prediction. Further studies exploring this potential in in vivo models are required. Molecular mechanisms may also provide tools for advances in experimental therapies, as they are responsible for modulating numerous oncogenic cellular processes. In a clinical study, NEAT1 knockdown in cervical cancer tissue samples resulted in inhibition of cell migration and increased apoptosis induction, indicating that these lncRNAs may serve as therapeutic targets (DU Y, et al., 2022).

In addition to their biological functions, the lncRNAs identified in this review demonstrate significant translational potential as biomarkers and therapeutic targets in CC. Regulatory axes such as GAS5/miR-21, HOTAIR/miR-29b/PTEN/PI3K, and NEAT1/miR-34a/LDHA have been consistently associated with key mechanisms underlying chemoresistance (WEN Q, et al., 2017; ZHANG W, et al., 2022; SHAO X, et al., 2021).

The GAS5/miR-21 axis plays a crucial role in regulating apoptosis and tumor suppressor pathways, suggesting its potential application as a predictive biomarker of response to DDP (WEN Q, et al., 2017; YAO T, et al., 2019). Similarly, the modulation of the miR-29b/PTEN/PI3K signaling pathway mediated by HOTAIR is strongly associated with proliferation, survival, and EMT, reinforcing its relevance as a potential therapeutic target (ZHANG W, et al., 2022). In addition, the NEAT1/miR-34a/LDHA axis highlights the importance of metabolic reprogramming, particularly through the regulation of glycolysis, in the development of chemoresistance (SHAO X, et al., 2021; PAVLOVA N and THOMPSON C, 2016).

From a translational perspective, the lncRNAs identified in this review represent promising candidates as both biomarkers and therapeutic targets in cervical cancer. Regulatory axes such as GAS5/miR-21, HOTAIR/miR-29b/PTEN/PI3K, and NEAT1/miR-34a/LDHA are consistently associated with key mechanisms underlying chemoresistance, including apoptosis inhibition, epithelial–mesenchymal transition, and metabolic reprogramming (WEN Q, et al., 2017; ZHANG L, et al., 2022; SHAO X, et al., 2021). These molecules may serve as predictive biomarkers of treatment response, particularly in cisplatin-based therapies, and could contribute to patient stratification in personalized medicine approaches (YAO T, et al., 2019; FANG X, et al., 2020). Furthermore, targeting lncRNA-mediated regulatory networks may represent a novel strategy to overcome drug resistance and improve therapeutic outcomes.

Study Limitations

This study has important limitations that should be considered. The exclusive use of in vitro experimental models restricts the generalizability of the findings, as these systems do not fully capture the complexity of the tumor microenvironment. Additionally, substantial heterogeneity was observed among the included studies regarding cell lines, drug concentrations, experimental conditions, and definitions of chemoresistance, which may affect the comparability and reproducibility of the results. The evidence is also limited to a narrow range

of chemotherapeutic agents, with a predominance of cisplatin-based studies, while other clinically relevant drugs remain underexplored. Moreover, the presence of studies with moderate risk of bias, as indicated by the JBI assessment, may influence the robustness of the conclusions. Therefore, further validation in in vivo models, clinical cohorts, and patient-derived tissues is necessary to confirm the translational applicability of these findings.

FINAL CONSIDERATIONS

The results suggest that lncRNAs such as MEG3 and GAS5 may influence treatment response by modulating critical pathways involved in proliferation, invasion, and drug resistance. Understanding these interactions may provide new biomarkers and potential therapeutic targets, reinforcing the importance of future investigations into the role of lncRNAs in cervical cancer progression and treatment resistance.

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REFERENCES

1. BHATTACHARJEE R, et al. Cellular landscaping of cisplatin resistance in cervical cancer. Biomed Pharmacother, 2022; 153: 113345.
2. BRAY F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018; 68(6): 394–424.
3. BRANDÃO HN, et al. Química e farmacologia de quimioterápicos antineoplásicos derivados de plantas. Quim Nova, 2010; 33(6): 1359–69.
4. CAO S, et al. Decreased expression of lncRNA GAS5 predicts a poor prognosis in cervical cancer. Int J Clin Exp Pathol, 2014; 7(10): 6776–83.
5. CHEN W, et al. Nomogram for prognosis of elderly patients with cervical cancer who receive combined radiotherapy. Sci Rep, 2023; 13(1): 13299.
6. DU Y, et al. LncRNA MEG3 promotes cisplatin sensitivity of cervical cancer cells by regulating the miR-21/PTEN axis. BMC Cancer, 2022; 22(1): 1145.
7. FANG X, et al. Low GAS5 expression may predict poor survival and cisplatin resistance in cervical cancer. Cell Death Dis, 2020; 11(7): 531.
8. FARZANEH M, et al. Emerging roles of the long non-coding RNA NEAT1 in gynecologic cancers. J Cell Commun Signal, 2023; 17(3): 531–47.
9. FENG L-L, et al. Expression of the lncRNA ZFAS1 in cervical cancer and its correlation with prognosis and chemosensitivity. Gene, 2019; 696: 105–12.
10. GHOSH S. Cisplatin: The first metal based anticancer drug. Bioorg Chem, 2019; 88: 102925.
11. GIDDINGS EL, et al. Mitochondrial ATP fuels ABC transporter-mediated drug efflux in cancer chemoresistance. Nat Commun, 2021; 12(1): 2804.
12. HE J, et al. Long non-coding RNA in cervical cancer: From biology to therapeutic opportunity. Biomed Pharmacother, 2020; 127: 110209.
13. HE S, et al. The role of the SOX9/lncRNA ANXA2P2/miR-361-3p/SOX9 regulatory loop in cervical cancer cell growth and resistance to cisplatin. Front Oncol, 2021; 11: 784525.
14. INSTITUTO NACIONAL DE CÂNCER (INCA). Estimativa 2023: incidência de câncer no Brasil. Rio de Janeiro: INCA, 2023.
15. JOHNSON CA, et al. Cervical cancer: An overview of pathophysiology and management. Semin Oncol Nurs, 2019; 35(2): 166–74.
16. LIU M, et al. Expression of micro-RNA-492 (MiR-492) in human cervical cancer cell lines is upregulated by transfection with wild-type P53, irradiation, and 5-fluorouracil treatment in vitro. Med Sci Monit, 2018; 24: 7750–8.

17. LIU MY, LI N. The diagnostic value of lncRNA HOTAIR for cervical carcinoma in vaginal discharge and serum. Medicine (Baltimore), 2023; 102(26): e34042.
18. LIU S, et al. SP1-induced lncRNA DUBR promotes stemness and oxaliplatin resistance of hepatocellular carcinoma via E2F1-CIP2A feedback. Cancer Lett, 2022; 528: 16–30.
19. LUO X, et al. Exosomal lncRNA HNF1A-AS1 affects cisplatin resistance in cervical cancer cells through regulating microRNA-34b/TUFT1 axis. Cancer Cell Int, 2019; 19: 323.
20. MAO B-D, et al. LINC00511 knockdown prevents cervical cancer cell proliferation and reduces resistance to paclitaxel. J Biosci, 2019; 44(2).
21. MARKMAN M. Advances in cervical cancer pharmacotherapies. Expert Rev Clin Pharmacol, 2014; 7(2): 219–23.
22. MECENAS P, et al. Effects of temperature and humidity on the spread of COVID-19: A systematic review. PLoS One, 2020; 15(9): e0238339.
23. METHLEY AM, et al. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv Res, 2014; 14(1): 579.
24. MODABBER N, et al. Evaluation of long non-coding RNA (lncRNA) in the pathogenesis of chemotherapy resistance in cervical cancer: diagnostic and prognostic approach. Mol Biotechnol, 2024; 66(10): 2751–2763.
25. ORGANIZAÇÃO PAN-AMERICANA DA SAÚDE (OPAS). Câncer do colo do útero. Washington, DC: OPAS.
26. PAGE MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 2021; 372: n71.
27. PAVLOVA NN, THOMPSON CB. The emerging hallmarks of cancer metabolism. Cell Metab, 2016; 23(1): 27–47.
28. QU S, et al. MiR-361-3p regulates liver tumor-initiating cells expansion and chemo-resistance. J Cancer, 2021; 12(5): 1483–92.
29. SAW PE, et al. Non-coding RNAs: the new central dogma of cancer biology. Sci China Life Sci, 2021; 64(1): 22–50.
30. SETHY C, KUNDU CN. 5-Fluorouracil (5-FU) resistance and the new strategy to enhance the sensitivity against cancer: Implication of DNA repair inhibition. Biomed Pharmacother, 2021; 137: 111285.
31. SHAO X, et al. Inhibition of lncRNA-NEAT1 sensitizes 5-Fu resistant cervical cancer cells through de-repressing the microRNA-34a/LDHA axis. Biosci Rep, 2021; 41(7).
32. SHEN C-J, et al. LncRNA PVT1 epigenetically silences miR-195 and modulates EMT and chemoresistance in cervical cancer cells. J Drug Target, 2017; 25(7): 637–44.
33. SWEEF O, et al. Decoding lncRNA in COPD: unveiling prognostic and diagnostic power and their driving role in lung cancer progression. Int J Mol Sci, 2024; 25(16): 9001.
34. WAN S, ZHAO H. Analysis of diagnostic and prognostic value of lncRNA MEG3 in cervical cancer. Oncol Lett, 2020; 20(5): 183.
35. WEN Q, et al. 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(6): 1096–108.
36. YAO T, et al. Growth arrest-specific 5 attenuates cisplatin-induced apoptosis in cervical cancer by regulating STAT3 signaling via miR-21. J Cell Physiol, 2019; 234(6): 9605–15.
37. YUAN LY, et al. Involvement of NEAT1/miR-133a axis in promoting cervical cancer progression via targeting SOX4. J Cell Physiol, 2019; 234(10): 18985–18993.
38. ZHANG L, et al. LncRNA SNHG5 promotes cervical cancer progression by regulating the miR-132/SOX4 pathway. Autoimmunity, 2021; 54(2): 88–96.
39. ZHANG W, et al. LncRNA HOTAIR promotes chemoresistance by facilitating epithelial to mesenchymal transition through miR-29b/PTEN/PI3K signaling in cervical cancer. Cells Tissues Organs, 2022; 211(1): 16–29.
40. ZHANG Y, WEN Y. The role of lncRNA NEAT1 in gastric cancer: tumor development and potential therapeutic target. Curr Pharm Des, 2023; 29(28): 2213–22.
41. ZHOU C, et al. Tislelizumab versus docetaxel in patients with previously treated advanced NSCLC (RATIONALE-303): A phase 3, open-label, randomized controlled trial. J Thorac Oncol, 2023; 18(1): 93–105.