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XIST as a modulator of chemotherapy resistance in cancers

XIST como modulador da resistência à quimioterapia em cânceres

XIST como modulador de la resistencia a la quimioterapia en cánceres

Eldevan da Silva Barbosa[1], Larissa Rodrigues de Sousa[2], Antonia Claudia da Conceição Palmeira[1], Ana Gabrielly de Melo Matos[2], Ramon da Silva de Oliveira[3], Rakel Gomes Mendonça[1], Matheus Silva Alves[5], Susanne Suely Santos da Fonseca[3], Eliel Barbosa Teixeira[3,4], Jaqueline Diniz Pinho[1,3].

ABSTRACT

Objective: This study aimed to summarize the main evidence highlighting XIST as a modulator of chemotherapy resistance in different tumor types. **Methods:** A literature review was conducted, selecting studies that correlate XIST with resistance to antineoplastic drugs. Bioinformatics tools, including NcPathName to identify target genes and the CIViC platform to associate these genes with chemoresistance, were used to investigate the role of XIST in different types of cancer. **Results:** XIST regulates genes associated with chemoresistance, such as PTEN, CDKN1A, CFLAR, MDM2, and ZEB1, which are involved in essential chemoresistance pathways. The interaction between XIST and these genes suggests specific molecular mechanisms behind resistance to agents like 5-fluorouracil in colorectal cancer. The literature suggests that XIST knockdown may be a promising strategy to overcome chemotherapy resistance. **Final considerations:** This study highlights the importance of exploring lncRNAs like XIST to better understand the mechanisms of chemotherapy resistance and develop more effective therapeutic approaches.

Keywords: Combined therapy, Biomarkers, Bioinformatics.

RESUMO

Objetivo: O presente estudo buscou sumarizar as principais evidências que destacam o XIST como modulador da resistência à quimioterapia em diferentes tipos tumorais. **Métodos:** Para tanto, foi realizado levantamento bibliográfico, selecionando estudos que correlacionam XIST com a resistência a drogas antineoplásicas. Utilizou-se ferramentas bioinformáticas, incluindo NcPathName para identificar genes alvo e a plataforma CIViC para associar esses genes com a quimiorresistência, o papel de XIST foi investigado em diferentes tipos de câncer. **Resultados:** XIST regula genes associados à resistência quimioterápica, como PTEN, CDKN1A, CFLAR, MDM2 e ZEB1, envolvidos em vias essenciais de quimiorresistência. A interação entre XIST e esses genes sugere mecanismos moleculares específicos por trás da resistência a agentes como o 5-fluorouracil, no câncer colorretal. A literatura sugere que o knockdown de XIST pode ser uma estratégia promissora para superar a resistência à quimioterapia. **Considerações finais:** Este estudo evidencia a importância de explorar lncRNAs como XIST para entender melhor os mecanismos de resistência à quimioterapia e desenvolver abordagens terapêuticas mais eficazes.

Palavras-chave: Terapia combinada, Biomarcadores, Bioinformática.

RESUMEN

Objetivo: El presente estudio buscó resumir las principales evidencias que destacan a XIST como modulador de la resistencia a la quimioterapia en diferentes tipos tumorales. **Métodos:** Para ello, se realizó una revisión

[1] Maranhão State University (UEMA), Zé Doca – MA.
[2] Graduate Program in Adult Health (PPGSAD/UFMA), São Luís – MA.
[3] Oncology Research Center, Federal University of Pará (NPO/UFPA), Belém - PA.
[4] Federal University of Amapá (UNIFAP), Macapá – AP.
[5] State University of the Tocantina Region of Maranhão, Imperatriz – MA.

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bibliográfica, seleccionando estudios que correlacionan XIST con la resistencia a fármacos antineoplásicos. Se utilizaron herramientas bioinformáticas, incluyendo NcPathName para identificar genes diana y la plataforma CIViC para asociar estos genes con la quimiorresistencia; se investigó el papel de XIST en diferentes tipos de cáncer. **Resultados:** XIST regula genes asociados con la resistencia quimioterápica, como PTEN, CDKN1A, CFLAR, MDM2 y ZEB1, involucrados en vías esenciales de quimiorresistencia. La interacción entre XIST y estos genes sugiere mecanismos moleculares específicos detrás de la resistencia a agentes como el 5-fluorouracilo en el cáncer colorrectal. La literatura sugiere que el knockdown de XIST puede ser una estrategia prometedora para superar la resistencia a la quimioterapia. **Consideraciones finales:** Este estudio evidencia la importancia de explorar lncRNAs como XIST para comprender mejor los mecanismos de resistencia a la quimioterapia y desarrollar enfoques terapéuticos más eficaces.

Palabras clave: Terapia combinada, Biomarcadores, Bioinformática.

INTRODUCTION

The cancer is a devastating disease that affects millions of people worldwide (SIEGEL RL, et al., 2023). Currently, the main types of treatment include surgery, radiotherapy, immunotherapy, targeted therapy, and chemotherapy (YAROMINA A, et al., 2020). It is known that chemotherapy is the most widely used treatment technique due to its low cost. Chemotherapeutic drugs have the ability to inhibit the progression of malignant neoplasms by targeting various pathways and mechanisms aimed at eliminating cancer cells (FANG X, et al., 2020).

However, some cells can acquire resistance to chemotherapeutic drugs, becoming a barrier in cancer treatment, which necessitates the gradual reduction of chemotherapy regimens or even their discontinuation, thereby limiting treatment efficacy (ROY M e MUKHERJEE S, 2014). In the context of chemoresistance, long non-coding RNAs (lncRNAs) stand out for their ability to confer resistance to antineoplastic drugs. These biomolecules can regulate gene expression through mechanisms such as histone modification, transcriptional regulation, and/or post-transcriptional regulation. They serve as key regulators of biological processes crucial for cancer progression by modulating gene expression and are considered potential biomarkers for malignant neoplasms (LUO Y, et al., 2021).

There is evidence that the lncRNA XIST may be involved in chemotherapy resistance in various types of cancer, such as breast cancer (BC) (ZHANG M, et al., 2020), colorectal cancer (CRC) (ZHANG R, et al., 2019) and non-small cell lung cancer (NSCLC) (XU X, et al., 2020), where its overexpression is associated with cisplatin resistance. O XIST can promote the proliferation of cells that develop chemotherapy resistance (LIU TT, et al., 2021). Its high expression is associated with unfavorable prognostic factors, including enhanced cell growth capacity, acting as an endogenous competing RNA (ceRNA) for miRNAs (XIA X, et al., 2022). Moreover, elevated expression of this lncRNA has been observed influencing chemotherapy resistance through autophagy induced via the miR-17/ATG7 signaling pathway (Sun W, et al., 2017).

Considering that chemoresistance plays a significant role in the failure of malignant neoplasm treatment, which consequently reduces patients' life expectancy, there is a need to understand the molecular mechanisms involved in chemotherapy resistance. This understanding aims to develop new strategies to prevent drug resistance (KUANG Y, et al., 2022). The aim of this study was to summarize the main evidence highlighting the lncRNA XIST as a modulator of chemotherapy resistance in different types of cancers. This lncRNA has the capacity to influence disease characteristics by acting as a miRNA sponge, altering cell proliferation, and interfering with apoptosis. Furthermore, the study investigated whether the target genes of this biomolecule are involved in the process of chemoresistance.

METHODS

Literature Review

The literature review investigated the role of XIST in chemotherapy resistance using the terms "XIST non-coding RNA AND chemoresistance" in databases such as the U.S. National Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO), ScienceDirect, and Scopus. Only original articles in English addressing this topic were considered, excluding abstracts, reports, reviews, monographs, and dissertations.

Identification of genes regulated by XIST

In the selected studies, it was found that XIST regulates several genes. However, there is a gap in information regarding its involvement in chemotherapy resistance. To fill this gap, an in silico enrichment analysis was conducted using the NcPathName tool (http://ncpath.pianlab.cn/#/Home), focusing on genes targeted by this lncRNA. Specifically, genes were selected based on experimental validation of their regulation by XIST and strong association with the studied lncRNA.

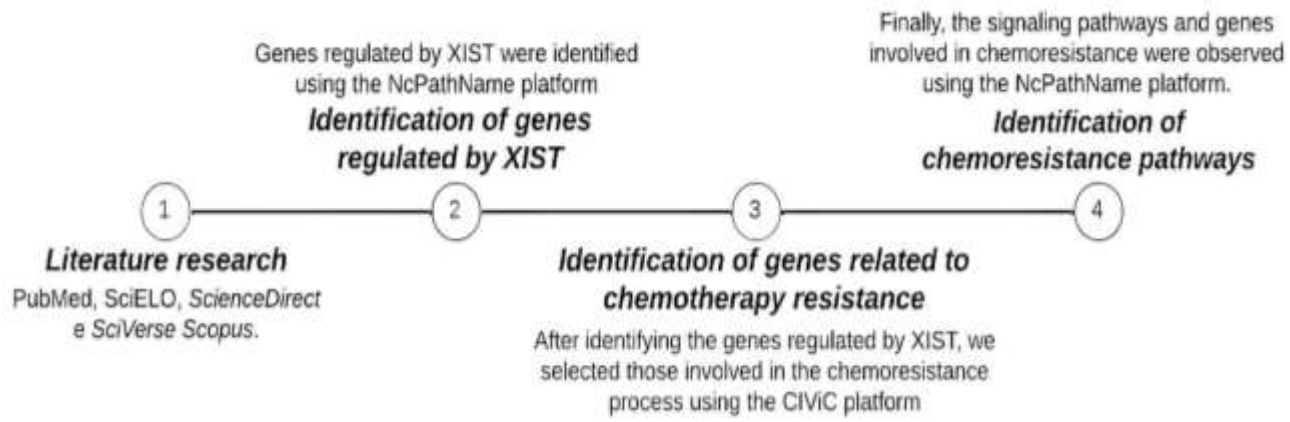
Identification of genes related to chemotherapy resistance

The genes regulated by XIST were analyzed using the CIViC platform (https://civicdb.org/evidence/706/summary) to identify their relevance to chemotherapy resistance. The selection of genes for inclusion in the study was based on evidence of their association with resistance to antineoplastic drugs.

Identification of pathways related to chemoresistance

The identification of pathways involved in the process of chemoresistance was conducted using the NcPathName platform, where the selected genes regulated by XIST were investigated.

Figure 1 - Methodological process.



Source: Barbosa ES, et al., 2024.

RESULTS

Survey and Analysis of Publications

We found 290 studies, from which we selected 13 articles correlating the lncRNA XIST with modulation of resistance to antineoplastic drugs (Supplementary Material - Table 1). In the investigation of target genes regulated by this lncRNA, 1693 genes were analyzed, of which only 12 were selected due to their association with resistance to antineoplastic drugs. Additionally, 83 pathways were identified, among which we selected five that play a role in the process of chemoresistance.

XIST and chemotherapy resistance in different types of cancer

Ovarian Cancer (OC)

XIST has been shown to influence chemotherapy resistance by acting as a ceRNA that binds to miR-506-3p and thereby indirectly modulates drug sensitivity-related gene expression in ovarian cancer (OC). In Figure 2A, it can be observed that high expression of XIST decreases miR-506-3p expression, which is a regulator of genes such as FOXP1. Knockdown of this miRNA leads to increased FOXP1 expression and consequently suppresses autophagy, contributing to chemotherapy resistance.

Additionally, FOXP1 influences the AKT/mTOR pathway, promoting cell survival and chemotherapy resistance. In this context, FOXP1 plays a significant role in regulating autophagy and carboplatin resistance

through the AKT/mTOR pathway. The interaction between XIST, miR-506-3p, and FOXP1 forms a regulatory axis that directly affects the sensitivity of ovarian cancer cells to carboplatin treatment (XIA X, et al., 2022).

Colorectal Cancer (CRC)

In the literature, XIST has been discussed in three studies on chemoresistance in CRC. Zhang R, et al. (2019) elucidated the XIST/miR-30a-5p/ROR1 axis, which promotes viability and proliferation of colorectal cells. XIST targets miR-30a-5p, so overexpression of this lncRNA reduces miR-30a-5p expression, activating the ROR1 protein and thereby making cells more resistant to antineoplastic drugs. This protein has been previously described to interact with pathways related to chemoresistance, such as PI3K/AKT/mTOR (SHORNING BY, et al., 2020) and the Wnt pathway (MENCK K, et al., 2021), suggesting that overexpression of XIST may activate pathways associated with chemoresistance (Figure 2B).

Similar results were described by Zheng H, et al. (2021), where XIST was shown to influence chemoresistance in CRC. Through regulation of tumor cell sensitivity to chemotherapeutic drugs like 5-FU/cisplatin and modulation of glycolysis, XIST played a significant role in treatment response. Additionally, its interaction with miR-137 reveals a complex network of molecular regulation directly affecting CRC resistance to therapies. These findings suggest XIST as a potential therapeutic target and underscore the importance of investigating the underlying molecular mechanisms of chemoresistance in CRC

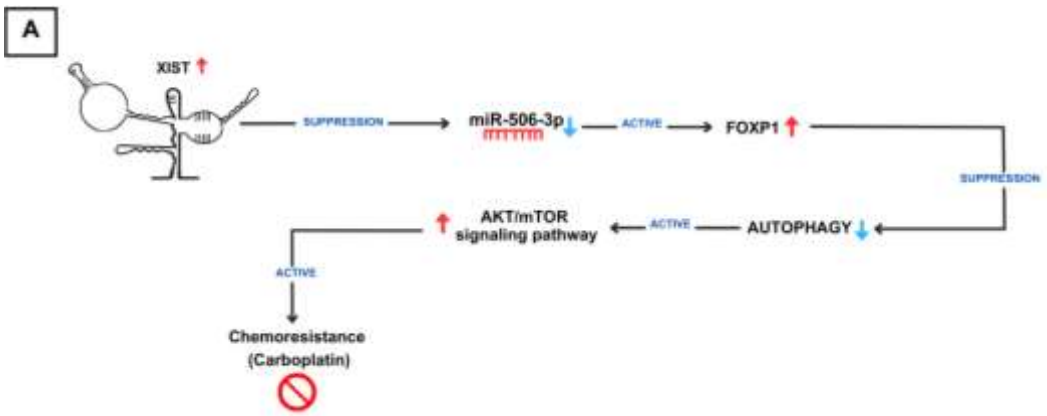
Non-Small Cell Lung Cancer (NSCLC)

XIST is highly expressed in NSCLC and is positively correlated with the TNM staging system and autophagy marker LC3B, suggesting its role in NSCLC development and progression (SUN W, et al., 2017). The association of XIST with cisplatin resistance in NSCLC patients is highlighted in four studies (Table 1), demonstrating that XIST inhibits miRNA-520 (LIU TT, et al., 2021) and miR-101-3p (HUA G, et al., 2021), thereby preventing regulation of their targets and impacting cisplatin sensitivity. Understanding XIST mechanisms is crucial for developing targeted therapies aimed at reversing chemoresistance.

In lung adenocarcinoma (AC), a specific subtype of NSCLC, XIST expression is positively regulated. Few studies report on the involvement of XIST in AC progression and chemoresistance. Sun W, et al. (2017) observed that decreasing XIST expression in A549/DDP cells through knockdown reduced chemotherapy resistance. It was found that XIST acts as a ceRNA, inhibiting let-7i, which in turn regulates the BAG-1 gene. BAG-1 is known to regulate apoptosis.

This regulation of let-7i/BAG-1 by XIST is proposed as a mechanism underlying cisplatin resistance (Figure 2C). Therefore, these findings suggest that the lncRNA XIST could be considered a promising biomarker for poor response to cisplatin, as well as a potential therapeutic target for chemotherapy. These discoveries have significant implications for the development of more effective therapeutic strategies against lung cancer.

Figure 2A - Schematic representation of the influence of XIST on the process of chemoresistance in ovarian cancer.



Source: ©Barbosa ES, et al., 2024 via Canva.com.

Figure 2B – Colorectal Cancer.

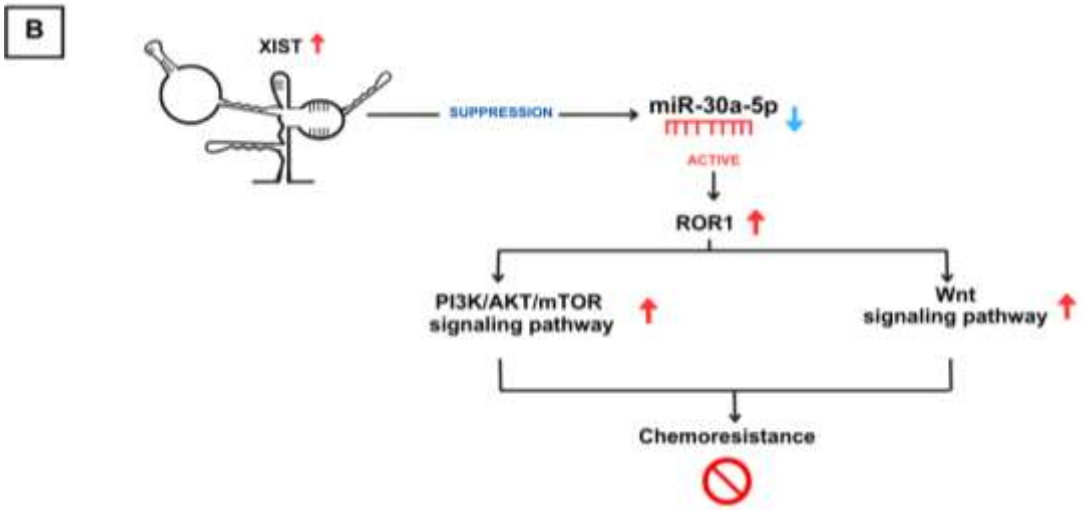


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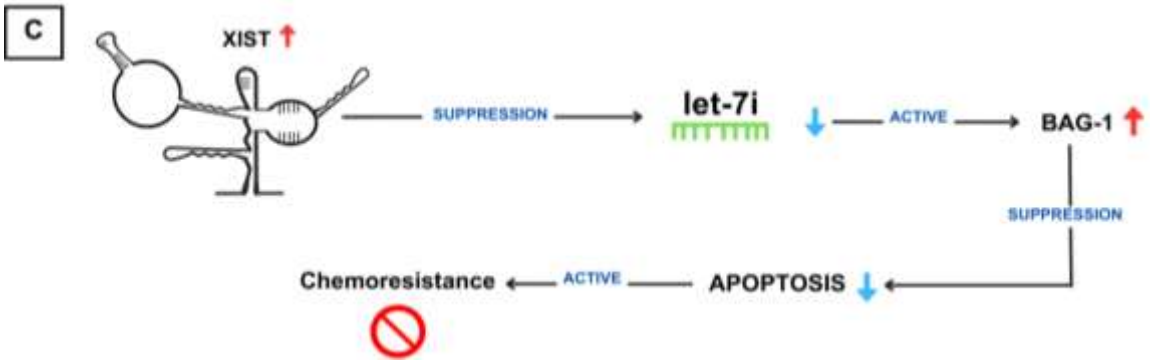
Figure 2C- Lung Adenocarcinoma.



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Breast Cancer (BC)

According to Zhang M, et al. (2020), overexpression of XIST promotes chemoresistance in breast cancer (BC) cells to doxorubicin. This occurs through XIST's ceRNA function, where it binds to miR-200c-3p and inhibits its expression. miR-200c-3p is a key regulator of gene expression. Thus, this complex (XIST/miR-200c-3p) significantly contributes to increased gene and protein expression of anillin (ANLN). Consequently, high ANLN expression is relevant for cell proliferation, inhibition of apoptosis, and resistance of cells to doxorubicin chemotherapy. Additionally, the study revealed that silencing XIST can inhibit cell proliferation and promote apoptosis in MDA-MB-231/ADM cells treated with doxorubicin (**Figure 3A**).

Consequently, the gene 53BP1 is associated with pathways that suppress tumor development. Although a direct relationship between 53BP1 and XIST has not been established, studies indicate that increased expression of XIST contributes to negative regulation of 53BP1, resulting in inhibition of apoptosis and increased cell proliferation. Additionally, research shows that negative regulation of the 53BP1 gene makes certain cells resistant to the chemotherapy drug 5-FU (YAO J, et al., 2017) (**Figure 3B**). Therefore, while more studies are needed to clearly analyze the relationship between XIST and 53BP1, studies suggest that XIST could be considered a potential biomarker to predict chemotherapy resistance in BC cases.

Glioma

According to the study conducted by Du P, et al. (2017), XIST is highly expressed in glioma tissues and cell lines, positively associated with worse prognostic factors, and linked to temozolomide (TMZ) resistance. As observed in the study, XIST inhibits the expression of miRNA-29c, thereby preventing its suppressive

function. Suppressed miR-29c can no longer inhibit the expression of Specificity Protein 1 (SP1). This, in turn, increases the expression of O-6-methylguanine-DNA methyltransferase (MGMT), promoting repair of alkylated DNA by TMZ (FUCHS RP, et al., 2021). Therefore, inhibition of miR-29c by XIST may lead to increased MGMT expression, resulting in enhanced ability of tumor cells to resist TMZ treatment due to effective repair of alkylated DNA (**Figure 3C**). The XIST/miR-29c relationship can thus regulate SP1 and MGMT expression, making cells resistant to TMZ. Therefore, XIST represents a potential therapeutic target for glioma treatment.

Nasopharyngeal Carcinoma (NPC)

Nasopharyngeal Carcinoma (NPC) is another malignant neoplasm that exhibits resistance to antineoplastic drugs modulated by XIST. Wang H, et al. (2019) found in their research that XIST was overexpressed in HNE1 cells treated with cisplatin (DDP). It was noted that the overexpression of this lncRNA negatively regulates the expression of Programmed Cell Death 4 (PDCD4) and Fas ligand (Fas-L), which are proteins involved in apoptosis-related processes (**Figure 3D**) (OLA MS, et al., 2011; ZHENG HX, et al., 2013). This explains how high expression of this lncRNA induces proliferation and inhibits apoptosis in HNE1/DDP cells. Therefore, XIST/PDCD4/Fas-L interactions may contribute to increased resistance to DDP, making them potential therapeutic targets. A inhibition of PDCD4 by XIST results in decreased expression of Fas-L. Consequently, apoptosis induced by Fas-L is reduced. This decrease in apoptosis can lead to increased resistance of the cells to DDP, which typically induces apoptosis.

Figure 3A - Schematic representation of the chemoresistance process in breast cancer. XIST/ANLN axis.

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Figure 3B- XIST/53BP1 axis.

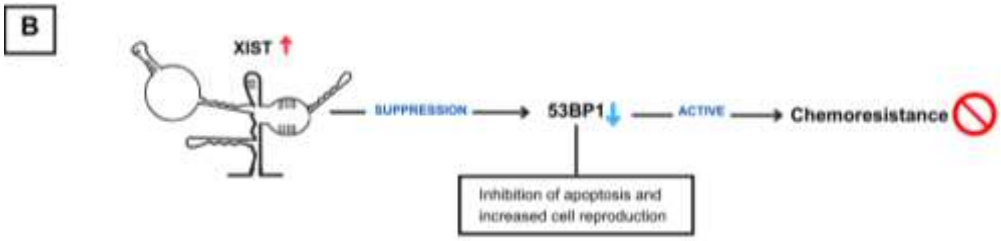

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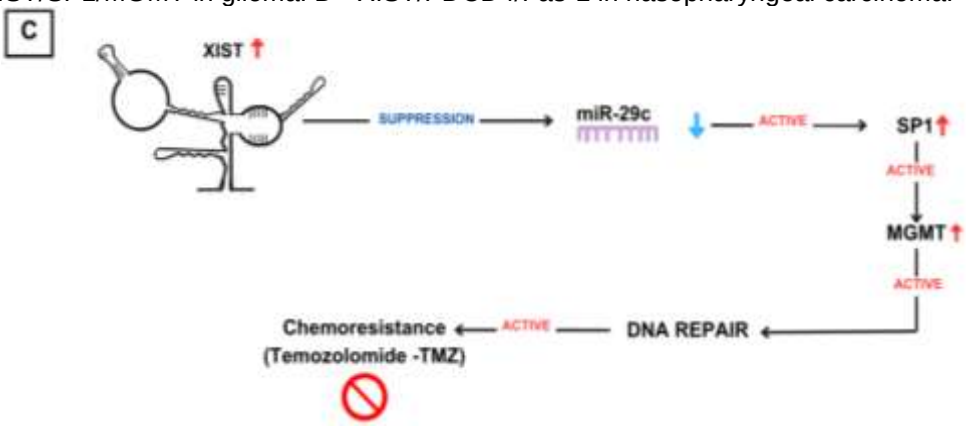
Figure 3C- XIST/SP1/MGMT in glioma. D - XIST/PDCD4/Fas-L in nasopharyngeal carcinoma.



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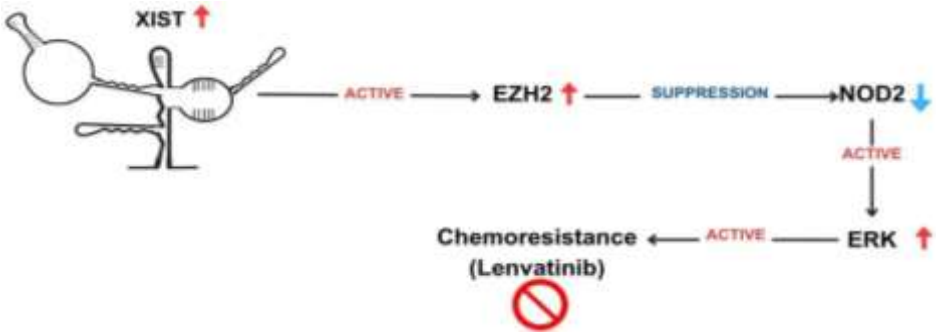
Hepatocellular Carcinoma (HCC)

In hepatocellular carcinoma (HCC), the XIST/EZH2/NOD2/ERK axis causes resistance to lenvatinib in HCC cells (DUAN A, et al., 2022). EZH2 (Enhancer of Zeste Homolog 2) is an enzyme involved in histone modification, where modifications can influence DNA accessibility (DEB G, et al., 2014). NOD2 (Nucleotide-binding Oligomerization Domain-containing protein 2) is a protein that plays a role in immune response and inflammation regulation (CORREA RG, et al., 2012), and ERK (Extracellular Signal-Regulated Kinase) is a kinase protein involved in signal transduction within the cell. It can activate or deactivate other proteins, affecting various cellular processes such as growth, survival, and differentiation (LAVOIE H, et al., 2020).

The interactions of these biomolecules were described by Duan A, et al. (2022) as a factor in determining chemoresistance. The process begins with high expression of XIST, which interacts with EZH2 to reduce the expression of NOD2. The negative regulation of NOD2 leads to the activation of ERK, thereby promoting chemoresistance (**Figure 4**).

Figure 4 - Schematic representation of the XIST/EZH2/NOD2/ERK pathway in the process of chemoresistance in hepatocellular carcinoma.



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Interaction of XIST with genes in pathways related to chemoresistance

In relation to XIST-targeted genes involved in resistance to anticancer drugs, we identified 12 specific genes. Among these, 9 showed resistance to only one chemotherapeutic agent, while 3 genes exhibited resistance to 2 different chemotherapeutics. Notably, the gene ZEB1 stood out as being associated with chemoresistance to 3 anticancer drugs. Within this set of 12 genes, we observed that 5 of them (PTEN, CDKN1A, CFLAR, MDM2, ZEB1) are involved in pathways related to chemoresistance. Additionally, upon analyzing the studied chemotherapeutic agents, 5-Fluorouracil was the most extensively discussed. Furthermore, the autophagy pathway proved relevant across different types of cancers, as shown in (**Table 1**).

Table 1 - Genes and pathways related to chemoresistance.

Gene	Tumor Type	Chemotherapeutics	Pathways
PTEN	Breast Cancer (BC)	Everolimus/Fulvestrant	Autophagy
NQO1	Lung Cancer (LC)	Amrubicin	-
CDKN1A	Colorectal Cancer (CRC)	5-Fluorouracil	Platinum drug resistance
ALCAM			-
ERBB4	Breast Cancer (BC)	Lapatinib/Trastuzumab	
IGF1R	Squamous Cell Lung Carcinoma (SCC)	Gefitinib	
CFLAR	Prostate Cancer (PCa)	Bicalutamide	Autophagy/Cell cycle/apoptosis
MDM2	Malignant Pleural Mesothelioma (MPM)	Pemetrexed/Cisplatin	Cell cycle/Platinum drug resistance
EPHB4	Colorectal Cancer (CRC)	Bevacizumab	-
CXCR4	Gastric Adenocarcinoma (GAC)	Docetaxel	
FGF2	Acute Myeloid Leukemia (AML)	Quizartinib	
ZEB1	Mantle Cell Lymphoma (MCL)	Doxorubicin/ Cytarabine/Gemcitabine	Ferroptosis/autophagy/ apoptosis

Source: Barbosa ES, et al., 2024.

Among the genes regulated by XIST, it is noted that CDKN1A and ALCAM are involved in resistance to the chemotherapy drug 5-fluorouracil in CRC. Resistance to this chemotherapy drug can result in treatment ineffectiveness, as it inhibits nucleic acid synthesis, interferes with cell replication, and restricts the synthesis of essential proteins for cell growth (SETHY C and KUNDU CN, 2021).

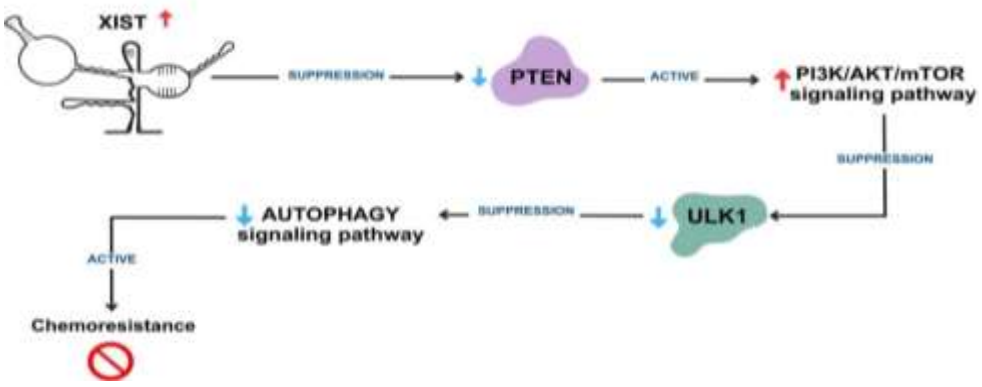
Therefore, the XIST/CDKN1A/ALCAM axis may induce resistance to 5-fluorouracil in CRC. ZEB1 was the only gene regulated by XIST that is associated with resistance to three antineoplastic drugs (doxorubicin, cytarabine, gemcitabine). This gene was found to be positively regulated in MCL cells, and its high expression is associated with factors of worse prognosis, activating genes involved in cell proliferation, anti-apoptosis, and modulating chemotherapy resistance. Conversely, its negative regulation increased chemosensitivity in MCL (SÁNCHEZ-TILLÓ E, et al., 2014). The above data suggest that regulation of ZEB1 by XIST may result in resistance to chemotherapy drugs.

In our study, we found that the genes PTEN, CFLAR, and ZEB1 are involved in the autophagy pathway and interact with the lncRNA XIST. This suggests that XIST regulates these genes, activating autophagy and thereby contributing to drug resistance.

Sun W, et al. (2017) support this idea, showing that the association between XIST and autophagy may influence chemotherapy resistance in NSCLC cells. PTEN, for example, inhibits the PI3K/Akt pathway, which suppresses tumor growth. Negative regulation of this pathway can contribute to treatment resistance in BC (GAO C, et al., 2019). CFLAR, in turn, is regulated by XIST and is associated with chemotherapy resistance through the apoptosis pathway.

Zhang H, et al. (2020) observed that the ferroptosis pathway is inhibited in GC, promoting tumor growth and reducing sensitivity to cisplatin and paclitaxel. In our study, we found that ZEB1, regulated by XIST, participates in this pathway. Other studies show that drug resistance can increase through inhibition of ferroptosis due to the action of exosomes derived from adipocytes and transfer of the MTTP gene (ZHANG Z, et al., 2023). XIST also regulates CFLAR and MDM2 genes in the cell cycle pathway. Proper regulation of the cell cycle is essential for tissue maintenance. Defects in this regulation can lead to uncontrolled cell proliferation or evasion of apoptosis, processes closely linked to cancer development (MAHESH AN, et al., 2022).

Figure 5 - Schematic representation of the XIST/PTEN/ULK1 pathway in the process of chemoresistance.



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In gastric cancer cells, reduced XIST levels resulted in an increase in cells in the G1 phase and a decrease in the S phase, suggesting that XIST promotes cell cycle progression (MA L, et al., 2017). MDM2, another gene regulated by XIST, is critical for tumorigenesis and is associated with unfavorable prognoses and advanced stages of cancer (ZAFAR A, et al., 2023). These findings indicate that XIST interacts with several genes important for anticancer drug resistance. We suggest that the XIST/PTEN/ULK1 axis influences this process. The XIST/PTEN/ULK1 complex begins with the overexpression of XIST, which negatively regulates the tumor suppressor PTEN. This negative regulation of PTEN triggers a cascade of activation in the PI3K/AKT/mTOR signaling pathway.

In this cascade, PI3K activates AKT, a protein kinase known to regulate various cellular processes such as survival, proliferation, and growth. AKT, in turn, activates mTOR, a kinase that controls cell growth, protein synthesis, and cellular response to nutrients and cellular stress.

Consequently, the autophagy pathway will be suppressed, as mTOR is a regulator that inhibits autophagy by suppressing key autophagy-regulating proteins such as ULK1 (PENG Y, et al., 2022). When these molecules are dysregulated, cells can acquire resistance to anticancer drugs (**Figure 5**).

Knockdown of XIST using siRNAs to reverse chemoresistance

In our hypothesis, we suggest that XIST may act as a modulator of genes involved in chemotherapy resistance. Recent studies show that lncRNAs can be silenced using small interfering RNAs (siRNAs). For instance, lncRNA-HOTAIR was silenced using this biomolecule, which consequently reduced doxorubicin resistance in breast cancer (LI Z, et al., 2019).

These data highlight the importance of targeting siRNAs for XIST knockdown. Previous research has explored this therapy to investigate XIST's role in resistance to anticancer drugs. Duan A, et al. (2022) conducted knockdown of this biomolecule and found that the half-maximal inhibitory concentration (IC50) decreased in hepatocellular carcinoma (HCC) cells treated with lenvatinib; conversely, overexpression of XIST increased IC50 in these cells.

Therefore, XIST overexpression in HCC cells contributes to lenvatinib resistance. In another study, XIST knockdown suppressed proliferation, thereby inhibiting colony formation in NSCLC cells through apoptosis. In other words, low XIST expression can induce apoptosis and suppress proliferation and colony formation in NSCLC cells (XU X, et al., 2020).

Although there are reports in the literature on the knockdown of this biomolecule using siRNAs, the mechanisms by which this therapy can prevent XIST from binding to genes involved in resistance to anticancer drugs are not yet fully understood. Therefore, we suggest targeting siRNAs to inhibit the overexpression of XIST, which would prevent the expression of genes regulated by this biomolecule, thereby avoiding the development of resistance to chemotherapy drugs.

FINAL CONSIDERATIONS

XIST is an lncRNA that participates in various biological processes, acting as a modulator of genes involved in chemotherapy resistance. Among the target genes of this biomolecule are PTEN, CDKN1A, CFLAR, MDM2, and ZEB1, which participate in pathways that induce chemoresistance in several cancers. Additionally, we suggest further research into the XIST/PTEN/ULK1 axis, which may induce resistance to anticancer drugs. Moreover, knocking down XIST using siRNAs is an ideal therapeutic mechanism to reverse resistance to anticancer drugs modulated by this lncRNA. It is important to note that the analyses were performed in silico, limiting the confirmation of new biomarkers. While bioinformatics tools are valuable, conducting laboratory experiments to support these findings remains crucial.

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