Review | Received 2 October 2023; Accepted 13 December 2023; Published 15 December 2023
https://doi.org/10.55092/exrna20230010

# The roles of lncRNA XIST in cancer chemoresistance

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**Abstract:** Background and Objective: Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs with a length of more than 200 nucleotides. Multiple studies have shown that lncRNAs are important molecules participating in cellular homeostasis. In fact, it is well known that lncRNAs are often dysregulated in diseases such as cancers. Cancer is a multistep and multifactorial disease. One of the processes that requires further attention is drug or chemoresistance in cancers. LncRNAs are involved in drug resistance as well. Among the different identified lncRNAs, the lncRNA XIST has emerged as a promising biotarget. Therefore, this review is aimed at reviewing the literature to identify the studies reporting on the involvement of XIST in chemoresistance. Key contents and Findings: XIST is involved in the mechanism of various chemotherapeutic drugs involving a lot of cancers. Most of the reported studies suggest a network of XIST-miRNA pathways that are altered in chemoresistant cancers. Conclusion: Based on the available literature, XIST is a promising target for chemoresistance. However, further in-depth studies are needed to validate these findings.

**Keywords:** XIST; lncRNA; resistance; chemotherapy; cancer

## 1. Introduction

Cancer is among the top causes of illness-related mortalities worldwide [1]. According to Globocan, it is estimated that in 2040, roughly 28.4 million new cancer cases will be reported., which is an increase of 47% compared to 2020 [1]. Despite all the efforts being made to detect cancer early, treatment of cancer and patient management, the number of cancer cases is still on the rise. One of the major hurdles of cancer management is the resistance of cancers to therapy, especially chemotherapy [2]. There are various drug resistance mechanisms that have been reported [2]. Apart from the standard molecular mechanisms, other mechanisms involving non-coding RNAs have come to light including the participation of long-non coding RNAs.

Recent advancements in molecular biology technology, specifically the application of next generation sequencing accompanying bioinformatic analysis have revealed the participation of non-coding RNA molecules in transcription, including long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs) [1]. LncRNAs are defined as a form of RNA having more than 200 nucleotides while belonging to regulatory ncRNAs along with small non-coding RNAs (small ncRNAs), which do not produce protein products as their names suggest [2,3]. Initially, lncRNAs were often tagged as 'transcriptional noise' because they were thought to be transcriptional by-products together with their inability in protein coding. However, their potential as a vital component in the regulation of gene expression at the level of epigenetic, transcriptional and post-transcriptional is eventually recognized by scientists. In addition, the participation of lncRNAs in the pathogenesis of cancers and diseases from the perspective of cell growth and differentiation is also being accepted by the research world now [4,5]. To date, lncRNAs have been discovered in all model organisms, with the latest lncRNA annotations reporting between 30,000 and 60,000 human lncRNAs but the numbers may increase in the near future [6,7]. Several studies have reported that lncRNAs are especially important in cancer biology including drug resistance mechanisms. Among the most widely studied lncRNAs, is the XIST lncRNA, which this review intends to focus on. Based on the literature, there has been an increasing number of publications focusing on XIST. Most of these studies have focused on the role of XIST in diseases including cancers and how it regulates drug resistance. This review aims to narrate the literature regarding the association of the lncRNA XIST and drug resistance in cancers.

## 2. Method

The methods are listed in Table 1.

**Table 1.** The method of the scoping review that was performed.

| Items | Specification |
|---|---|
| Date of Search (specified to date, month and year) | Until 21 September 2023 |
| Databases and other sources searched | Pubmed |
| Search terms used (including MeSH and free text search terms and filters) | XIST, lncRNA, drug, resistance, cancer |
| Timeframe | Include all with the relevant terms |
| Inclusion and exclusion criteria (study type, language restrictions *etc.*) | Only English articles are considered |
| Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, *etc.*) | Independently |
| Any additional considerations, if applicable | NA |

## 3. LncRNA XIST and cancer

Initially, Ballabio and team found the human XIST gene through a cDNA library screening and then classified it alongside Carolyn J. Brown and Hunt Willard, whereby only the inactive X chromosome of the placental mammals expresses this gene from the X-inactivation center (Xic) [8]. XIST is known to encode a 17-kb lncRNA that is maintained in the nucleus despite being capped, spliced and poly-adenylated [9].

The epigenetic process of X-chromosome inactivation (XCI) which balances the dosage of X-linked genes in female (XX) and male (XY) mammals is governed by XIST RNA [10]. Herein, XCI relies on the lncRNA XIST, which wraps the inactive X chromosome in cis and initiates a series of events that eventually result in chromosome-wide transcriptional silencing that is permanent throughout an organism's lifespan [11]. Intriguingly, lncRNA XIST has been suggested to be employed as a female-specific marker in individual sex determination of forensic science based on biological fluid evidence (saliva, peripheral blood and menstrual blood), as XIST is discovered to be solely expressed in female body fluid samples while none in male samples [12]. The mechanism by which XIST is transcribed involves the recruitment of the PRC2 complex, which binds to RepA [13]. This will in turn mediate H3K27me3, as shown in Figure 1. Nevertheless, in female-related cancers, the expression of XIST is generally downregulated [14]. In males, however, although it is known to be expressed in germ cells, it has been shown that certain cancers in males also somatically express XIST [15,16]. In male cancers, it is suggested that the somatic expression of XIST could be due to epigenetic mechanisms such as DNA methylation and chromatin accessibility in chromosome X [15].

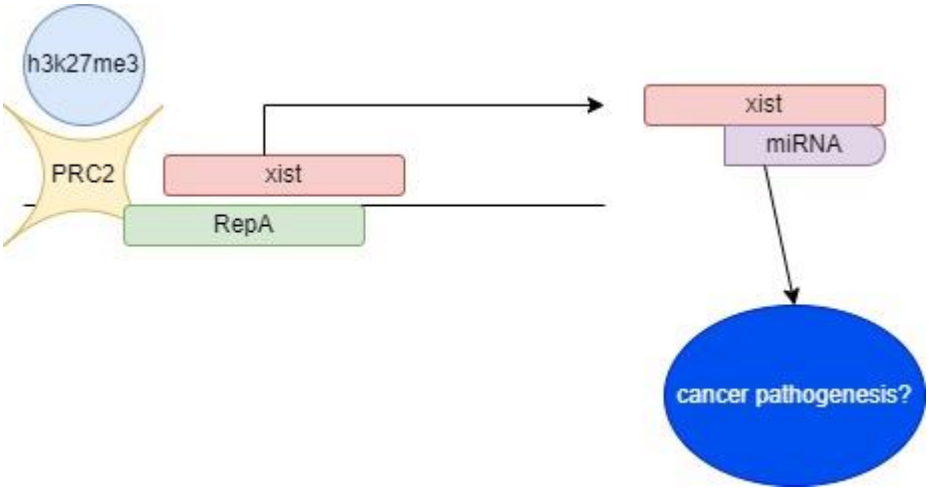


**Figure 1.** Proposed transcription process of XIST.

The past few years have seen remarkable advances regarding the roles of XIST in cancer biology. XIST is one of the most well-studied lncRNAs with its detection in a variety of human neoplasia and its upregulation or downregulation decides its role as an oncogene or tumor suppressor in the respective cancers [17]. According to the GEPIA database, the expression of XIST varies between cancers (http://gepia.cancer-pku.cn/index.html, accessed on 21 September 2023). Researchers have discovered that XIST has the potential to promote

tumor growth in gastric cancer [18,19], colon cancer [20], pancreatic cancer [21], hepatocellular carcinoma [22,23], nasopharyngeal carcinoma [24], glioblastoma [25], bladder cancer [26,27], non-small-cell lung cancer [28,29] and papillary thyroid carcinoma [30]. On the other hand, other studies claim that XIST exerts tumor-suppressive effects in osteosarcoma [31], prostate cancer [32], cervical squamous carcinoma [33] and breast cancer [34]. Based on the mentioned findings, of particular interest is the role of XIST as a miRNA sponge or competing endogenous RNA (ceRNA), as such XIST can act as a competitive inhibitor to regulate the expression of the interest miRNA which then limits the ability of the miRNA to bind to its target genes. Some pathological changes in the tumor environment, for instance, proliferation, migration, invasion, metastasis and chemosensitivity could be affected by the ceRNA network formed by XIST due to the changes in the level of the miRNA target genes [18,19,35]. The growing body of evidence on the link between XIST and cancer is promising, yet not much is known regarding its significance in cancer therapies. The general expression of XIST in various cancers as reported by the genome cancer atlas (TCGA) is shown in Figure 2.

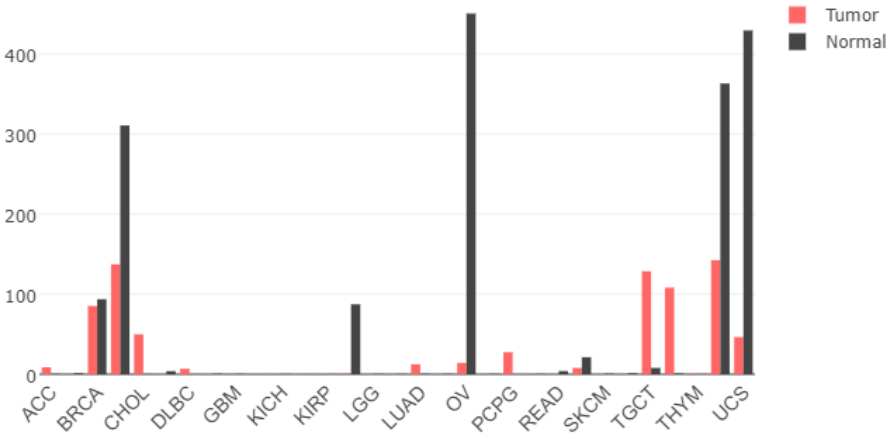


**Figure 2.** Overall expression of XIST in multiple cancers based on the TCGA dataset. Publicly available data accessed from the GEPIA website [36] (http://gepia.cancer-pku.cn/index.html, accessed on 21 September 2023).

## 4. XIST and antitumor antibiotics

LncRNAs have been shown to mediate carcinogenesis throughout the last decade and have also been discovered to be involved in drug resistance or sensitivity of tumor cells [36]. Antitumor antibiotics are a class of drugs that are commonly used to treat cancers by interfering with their DNA/RNA. In breast cancer cases, chemotherapy is essential for clinically successful treatments together with surgery, endocrine therapy and targeted therapy, specifically doxorubicin (an anthracycline chemotherapy drug). However, it is reported that XIST inhibited apoptosis of doxorubicin-treated BC cells (MDA-MB-231/ADM) by acting as a ceRNA to suppress miR-200c-3p [37], which then upregulated both gene and protein expression of ANLN (anillin actin-binding protein). Other than

demonstrating that both XIST and ANLN were abundant in doxorubicin-resistant BC cells, these findings also suggested that XIST overexpression stimulated cell proliferation and at the same time inhibited apoptosis of doxorubicin-treated BC cells by elevating ANLN expression [37]. Elevated ANLN expression is shown to promote apoptosis and enhance the expression of cleaved-caspase-3 in doxorubicin-treated BC cells [37].

Besides, XIST is revealed to form a ceRNA network with miR-29a and MYC in acute myeloid leukemia (AML) cells as well, in which XIST is negatively associated with miR-29a while positively correlated with MYC [38]. XIST silencing reduced mRNA and protein expression of MYC, leading to increased sensitivity of AML bone marrow cells to doxorubicin with facilitated apoptosis [38]. This could be the detrimental effect of downregulated MYC, as evidenced by elevated protein expression of cleaved-caspase-3 and Bax (both are pro-apoptotic genes) accompanied by reduced protein expression of Bcl-2 (anti-apoptotic gene) [38].

XIST has also been linked to treatment resistance in ovarian cancer [39,40]. Researchers discovered that XIST enhances the stability of KMT2C mRNA, which in turn sensitizes ovarian cancer cells and tissues to paclitaxel (microtubule-stabilizing drug) via miR-93-5p suppression [40]. This is supported by *in vivo* results that showed overexpressed XIST markedly halted the growth of ovarian cancer stem cells while elevating KMT2C expression [40].

## 5. XIST and alkylating agents

Alkylating agents are another class of commonly used chemotherapy drugs. XIST is extensively studied to shed light on its possible role in cisplatin-resistant lung cancer cells. Upregulation of XIST is observed in lung adenocarcinoma (LAD) cells and tissues that developed cisplatin resistance, whereby XIST sponged let-7i which targets BAG-1 (BCL2-associated athanogene 1) protein [41]. As BAG-1 protein is a well-known essential component for preventing cells from apoptotic stimuli, aberrant activation of XIST/let-7i/BAG-1 pathway is suggested to be the culprit of cisplatin resistance in LAD, mainly through facilitated proliferation and reduced apoptotic ability [41]. Similarly, XIST has also been shown to be a potential regulator for cisplatin resistance in non-small cell lung cancer (NSCLC). It is reported that XIST may potentially contribute to the cisplatin resistance of NSCLC cells by activating autophagy [42]. The team has proved that there is a positive association between the expression of XIST and ATG7 (autophagy-related 7) protein, while miR-17 is negatively correlated with XIST. Biological experiments successfully demonstrated that activation of XIST/miR-17/ATG7 pathway may be responsible for the chemoresistance progression in cisplatin-treated NSCLC cells, as evidenced by ATG7 being an important protein indicator for autophagy [42]. Besides, the sponging effect of XIST to miRNA-144-3p may have an impact on the sensitivity of NSCLC cells and tissues towards cisplatin [43]. In support of this, silencing of XIST is shown to hinder cell survival, proliferation, migration and invasion in NSCLC. At the same time, cell apoptosis is induced accompanied by lowered MDR1 (multidrug resistance-1) and MRP1 (multidrug resistance-

associated protein 1) expression. However, these effects could be restored with miR-144-3p inhibitor transfection [43].

The relationship of XIST in cisplatin treatment among NSCLC patients is further studied via bioinformatics prediction. Conversely, XIST is hypothesized to be capable of modulating mRNA BAX (Bcl-2-associated X protein) expression by functioning as a miRNA-520 sponge in NSCLC cells, which in turn could be useful in preventing cisplatin resistance [44]. It is worth noting that upregulation of BAX not only might contribute to activation of p53-promoted apoptosis but also might act on tumor-infiltrating immune cells (B cell, CD8 + T cell, CD4 + T cell, macrophage, neutrophil and dendritic cell) which could be a significant helper in immunotherapy efficacy among NSCLC patients [44]. Instead of targeting miRNA, XIST is reported to interact with SMAD2 (mothers against decapentaplegic homolog 2) protein as well by hindering its nuclear translocation from the cytoplasm in NSCLC cells [45]. As a result, inhibited SMAD2-dependent gene transcription is observed, particularly NLRP3 (NLR family pyrin domain containing 3) and p53 which play vital roles in pyroptosis and apoptosis respectively. It is worth noting that the team proposed the occurrence of pyroptosis is solely independent as it is only induced after cisplatin treatment, without being affected by XIST which plays a part in mediating apoptosis in NSCLC cells. Thus, this pathway has shown potential in regulating proliferation and chemoresistance to cisplatin in NSCLC cells [45].

Current evidence shows that overexpression of XIST in malignant melanoma (MM) tissues and cell lines is responsible for cellular oxaliplatin resistance in addition to increased proliferation and migration of MM [46]. By informatic analysis, the miRNA that may be involved is miR-21 which is predicted to bind with XIST at 3'-UTR and target the PI3KR1 gene at 3'-UTR respectively. Likewise, the sponging of XIST to miR-21 eventually led to the upregulated mRNA and protein levels of PI3KR1. The researchers also proposed that inactivated PI3K/AKT apoptosis signaling could play a part in the oxaliplatin resistance of MM cells [46]. Another group of investigators also proved the role of XIST in resisting cisplatin treatment by sponging miR-27b-3p in oral squamous cell carcinoma (OSCC). Particularly, overexpression of XIST is exclusively related to increased proliferation and cisplatin resistance while hampered apoptosis in OSCC cells [47].

XIST has also been linked to be a potential sponge for multiple miRNAs that could play a critical role in the chemotherapy resistance of malignant brain tumors. A group of researchers has found that upregulated XIST triggered protein expression of both SP1 (specificity protein 1) and MGMT (methylguanine-DNA methyltransferase) by directly binding to miR-29c, ultimately suppressing the response of glioma cells to temozolomide (TMZ), which is a common alkylating agent in brain tumor chemotherapy [48]. Moreover, the team has proposed that the MMR (DNA mismatch repair) pathway is involved in mediating the TMZ resistance as the protein levels of MSH6 (MutS homolog 6), SP1 and MGMT are found to be positively correlated with XIST expression in TMZ-resistant glioma cell lines. The existing correlation of MSH6, SP1 and MGMT with XIST/miR-29c served as an indicator for the involvement of the MMR pathway in TMZ-resistant glioma cells [48]. In another recent study, XIST was reported to exert its sponging effect on miR-152 which led to upregulation of KLF4 (Kruppel-like factor 4) protein expression via induction of SRC-1

(steroid receptor coactivator-1) in glioblastoma [49]. The researchers suggested XIST RNA expression is more likely to be enhanced by SRC-1 at the posttranscriptional level instead of increasing its transcriptional activity. XIST RNA is also shown to be stabilized by SRC-1, which might in turn promote stem-like characteristics of glioblastoma cells through activation of XIST/miR-152/KLF4 pathway. Subsequently, it is demonstrated that the knockdown of SRC-1 ultimately improved the sensitivity of glioblastoma cell lines treated with TMZ and sorafenib with a significantly reduced proliferation rate [49]. A study on XIST expression in mesenchymal-subtype glioblastomas showed that XIST mediated glucose metabolism as evidenced by its correlation with mRNA expressions and protein levels of both GLUT1 (glucose transporter 1) and GLUT3 (glucose transporter 3) [50]. Particularly, XIST is revealed to sponge miR-126, which then upregulates the protein level of IRS1 (insulin receptor substrate 1). Other than proving miR-126-dependent IRS1/PI3K-Akt pathway in controlling the glucose metabolism and tumor aggressiveness, significantly decreased migration, invasion and resistance to apoptosis in glioma cells by knockdown of XIST is also revealed [50].

## 6. XIST and antimetabolites

One of the most widely used drugs to treat colorectal cancer (CRC), is 5-fluorouracil, an antimetabolite drug. The network interaction axis of XIST/miR-30a-5p/ROR1 (receptor-tyrosine-kinase-like orphan receptor 1) is shown to enhance the resistance of CRC cells towards the designated chemotherapy drugs (5-fluorouracil, cisplatin, mitomycin and adriamycin) with increased viability and proliferation of tumor cells [51]. Interestingly, the team has also proved that the addition of atractylenolide II (Chinese drug) as combined therapy treatment led to attenuated chemoresistance of CRC cells, whereby both XIST and ROR1 are downregulated and miR-30a-5p is upregulated [51].

Subsequently, via bioinformatics prediction, a group of investigators also demonstrated the roles of XIST in resisting chemotherapy besides regulating CRC growth and metastasis by forming a ceRNA network with miR-125b-2-3p and WEE1 (WEE1 G2 checkpoint kinase) protein [52]. In vitro results concluded that upregulation of miR-125b-2-3p significantly sensitized CRC-resistant cell lines to fluorouracil and oxaliplatin, in which both the cell lines previously had noticeable MDR1 (multidrug resistance 1) overexpression despite specific mechanism remained undiscovered [52]. In another recent study, it was reported that glycolysis could also play a part in mediating the chemoresistance of CRC cells towards 5-fluorouracil/cisplatin treatment with the participation of XIST [53]. XIST is shown to be positively correlated with the ratio of PKM2 (pyruvate kinase M2) mRNA and PKM1 (pyruvate kinase M1) mRNA, while negatively correlated with miR-137 at the same time. It is observed that activation of the aforementioned axis enhanced 5-fluorouracil/cisplatin chemoresistance and glycolysis along with increased proliferation, migration and invasion of CRC cells [53]. Moreover, XIST is found to be upregulated in 5-fluorouracil-resistant CRC cells and tissues, whereby a positive correlation between XIST and thymidylate synthase enzyme is revealed. Since 5-fluorouracil-based chemotherapy mainly targets thymidylate

synthase enzyme, knockdown of XIST accompanied by hampered thymidylate synthase enzyme could be a possible break point for 5-fluorouracil treatment failure [54].

## 7. Clinical trials utilizing XIST

Based on our search using the clinical trials database, clinicaltrials.gov (accessed on 5 December 2023), there are only two clinical trials that are focused on XIST. The first clinical trial, NCT04288739, is based in Egypt, and the status is currently unknown. This clinical trial is aimed at investigating the relationship between XIST and immunophenotyping in acute myeloid leukemia (AML) patients. The second clinical trial, NCT04093609, is also based in Egypt. This study focuses on identifying XIST gene deletion in breast cancer patients and how it relates to therapy response. This clinical study also has an unknown status at the date of access.

**Table 2.** Involvement of XIST in treatment resistance of human cancers.

| Type of cancer | Expression of XIST | Intersection molecules | Sample type | Resistant to (chemotherapy) | Reference |
|---|---|---|---|---|---|
| Breast cancer | Up | miR-200c-3p/ANLN | Cell line | Doxorubicin | [37] |
| Ovarian cancer | Down | miR-93-5p/ KMT2C | Tissue and cell line | Paclitaxel | [40] |
| Colorectal cancer | Up | miR-30a-5p/ROR1 | Tissue and cell line | 5-fluorouracil, cisplatin, mitomycin and adriamycin | [51] |
| Colorectal cancer | Up | miR-125b-2-3/WEE1 | Tissue and cell line | Fluorouracil and oxaliplatin | [52] |
| Colorectal cancer | Up | miR-137/PKM | Tissue and cell line | 5-fluorouracil/cisplatin | [53] |
| Colorectal cancer | Up | Thymidylate synthase enzyme | Tissue and cell line | 5-fluorouracil | [54] |
| Lung adenocarcinoma | Up | let-7i/BAG-1 | Tissue and cell line | Cisplatin | [41] |
| Non-small cell lung cancer | Up | miR-17/ATG7 | Tissue and cell line | Cisplatin | [42] |
| Non-small cell lung cancer | Down | miRNA-520/BAX | Tissue and cell line | Cisplatin | [44] |
| Non-small cell lung cancer | Up | SMAD2/ NLRP3/p53 | Tissue and cell line | Cisplatin | [45] |
| Glioma | Up | miR-29c/SP1/MGMT | Tissue and cell line | Temozolomide | [48] |
| Glioblastoma | Up | SRC-1/miR-152/KLF4 | Tissue and cell line | Temozolomide | [49] |
| Malignant melanoma | Up | miR-21/PI3KR1 | Tissue and cell line | Oxaliplatin | [46] |
| Oral squamous cell carcinoma | Up | miR-27b-3p | Tissue and cell line | Cisplatin | [47] |
| Acute myeloid leukemia | Up | miR-29a/MYC | Cell line | Doxorubicin | [38] |

## 8. Perspective and future directions

The information on the roles of XIST in the drug response of human cancers acquired from available articles is summarized in Table 2. These studies show that XIST regulates chemoresistance by serving as a sponge for different miRNAs. This will later in turn affect the transcription of key regulator genes that are involved in chemoresistance. With present technologies, it is anticipated that all binding targets of XIST have yet to be discovered completely. Hence, advanced technologies such as bioinformatic analysis, as opposed to the

conventional methods, can aid in finding probable interactions of XIST with other molecules. To acquire a reliable result, it is also necessary to validate the results produced from bioinformatic analysis by completing *in vivo* and *in vitro* validation experiments. Due to the ambiguous nature of XIST, the determination of the underlying mechanism of XIST in chemoresistance may be challenging but a worthwhile approach.

## 9. Conclusion

In conclusion, XIST provides a promising approach to target chemoresistance in cancers and its mechanism should be further elucidated in depth.

## Conflicts of interests

Authors declare no conflict of interest.

## Authors' contribution

LCI, SFM and NA drafted and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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