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Review

Beyond X-Chromosome Inactivation: The Oncogenic Facet of XIST in Human Cancers

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Long-non coding RNAs (LncRNAs) constitute a wide and extremely diverse family of RNA transcripts that are greater than 200 base pairs in length and are not translated into proteins. X-inactive specific transcript (XIST) was the first long non-coding RNA to be discovered, back in 1991. Its function in X-chromosome inactivation has been extensively studied for three decades, though other functional roles of XIST that involve a variety of fascinating mechanisms remain to be elucidated. Here, we review the emerging oncogenic role of XIST in various human cancers.

Key Words: X chromosome inactivation, XIST, LncRNA, CeRNA, Human cancer; miRNA

INTRODUCTION

The specific transcript involved in X chromosome inactivation is called X-inactive specific transcript (XIST), and it was the first long non-coding RNA to be identified, by Brown et al. in 1991. XIST is thought to be a critical determinant for X chromosome inactivation. It is a 17,000-base-pair long non-coding RNA (lncRNA) that is spliced, polyadenylated, and constrained to the nucleus, and it does not produce a protein product.

A recent round of studies has provided new evidence of an oncogenic role of XIST in several cancers (Fig. 1). XIST has been shown to be highly expressed in tumor tissues compared to normal tissues. Furthermore, many reports have underlined its clinical significance and suggested that XIST can serve as a prognostic marker for many tumors. Mechanistically, XIST exerts its oncogenic effects by acting mainly as a competing endogenous RNA (ceRNA); the mechanism of ceRNAs is a relatively new epigenetic concept, which suggests that a competition might exist between a microRNA (miRNA) and a lncRNA leading to the upregulation of a target gene (Thomson and Dinger, 2016). In fact, XIST seems to act as a sponge for a plethora of miRNAs in various tumors. As the ceRNA concept provides new insights and indicates a more sophisticated post-transcriptional gene regulation role of XIST, via miRNA sequestration, deciphering the newly emerging function of XIST is needed now more than ever.

This review provides an overview of the auspicious sponge role of XIST in cancer, as summarized in Table 1.

Lung cancer

Recent studies have consolidated previous findings establishing a correlation between the XIST lncRNA and lung cancer, where XIST has been proven to be very important

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Table 1. Functional characterization of XIST in human cancers

Cancer type	XIST expression level	XIST molecular target (s)	Downstream genes	Effect on cancer progression and metastasis	Functional role of XIST (oncogene/ tumor suppressor)	References
Non-small-cell lung cancer	Upregulated	miR-367 and miR-141	ZEB2	↑ TGF-β induced EMT	Oncogene	Li et al., 2018
	Upregulated	miR-137	PXN/Notch-1	↑ Proliferation ↑ Invasion	Oncogene	Jiang et al., 2018 Wang et al., 2018
	Upregulated	miR-186-5p	Unknown	↑ Cell viability ↑ Invasion ↓ Apoptosis	Oncogene	Wang et al., 2017a
	Upregulated	miR-449a	Bcl-2	↑ Cell proliferation ↑ Cell migration and invasion ↓ Apoptosis	Oncogene	Zhang et al., 2017
	Upregulated	miR-374a	LARP1	↑ Cell growth ↑ Migration ↑ Invasion ↑ Tumorigenicity	Oncogene	Xu et al., 2017b
	Upregulated	EZH2	KLF2	↑ Cell proliferation ↑ Migration ↑ Invasion ↑ Tumorigenicity Poor prognosis	Oncogene	Fang et al., 2016
	Upregulated	miR-17	ATG7	↑ Autophagy ↑ TNM stage ↑ Chemoresistance	Oncogene	Sun et al., 2017b
	Upregulated	Let-7i	BAG-1	↑ Resistance to cisplatin	Oncogene	Sun et al., 2017a
	Upregulated	miR-140	iASPP	↑ Cell proliferation ↓ Apoptosis ↑ Metastasis	Oncogene	Tang et al., 2017
Colorectal and Gastric cancer	Upregulated	miR-185	TGF-β1	↑ Cell growth ↑ GC progression	Oncogene	Zhang et al., 2018
	Upregulated	miR-34a	WNT1/ β-catenin	↑ Cell proliferation ↑ Invasion	Oncogene	Sun et al., 2018a
	Upregulated	miR-137	EZH2	↑ EMT ↑ Invasion	Oncogene	Liu et al., 2018a
	Upregulated	miR-497	MACC1	↑ Cell cycle progression ↑ Invasion	Oncogene	Ma et al., 2017b
	Upregulated	miR-200b-3p	ZEB1	↑ Cell proliferation ↑ Invasion ↑ EMT ↑ Stemness ↓ Overall survival	Oncogene	Chen et al., 2017
	Upregulated	miR-132-3p	MAPK1	↑ Cell cycle progression	Oncogene	Song et al., 2017
	Upregulated	Unknown	TS	↓ 5-FU cytotoxicity Poor therapeutic efficacy	Oncogene	Xiao et al., 2017
	Upregulation	miR-101	EZH2	↑ Tumor aggressiveness Poor patient survival	Oncogene	Chen et al., 2016

Table 1. Functional characterization of XIST in human cancers (Continued)

Cancer type	XIST expression level	XIST molecular target (s)	Downstream genes	Effect on cancer progression and metastasis	Functional role of XIST (oncogene/ tumor suppressor)	References
Hepatic cancer	Upregulated	miR-194-5p	MAPK1	↑ Cell proliferation ↑ Migrasion ↑ Invation	Oncogene	Kong et al., 2018
	Downregulated	miR-181a	PTEN	↓ Cell proliferation ↓ Invasion	Tumor suppressor	Chang et al., 2017
	Upregulated	miR-139-5p	PDK1	↑ Cell cycle progression ↓ Apoptosis	Oncogene	Mo et al., 2017
	Downregulated	miR-92b	Smad7	↓ Cell proliferation ↓ Metastasis	Tumor suppressor	Zhuang et al., 2016
Breast cancer	Downregulated	miR-155	CDX1	↓ Cell growth ↓ Migration ↓ Invasion	Tumor suppressor	Zheng et al., 2018
	Downregulated	PHLPP1	AKT	↓ Cell viability	Tumor suppressor	Huang et al., 2016
Glioma	Upregulated	miR-137	Rac1	↑ Cell proliferation ↑ Tumorigenesis	Oncogene	Wang et al., 2017b
	Upregulated	miR-29c	MSH6/SP1/ MGMT	↑ Chemoresistance to TMZ	Oncogene	Du et al., 2017
	Upregulated	miR-137	FOXC1/ZO-2	↑ Angiogenesis ↓ Blood-tumor permeability	Oncogene	Yu et al., 2017
	Upregulated	miR-429	Unknown	↑ Tumorigenicity ↑ Angiogenesis ↑ Metastasis	Oncogene	Cheng et al., 2017
	Upregulated	miR-152	KLF4	↑ Cell proliferation ↑ Migration ↑ Invasion ↓ Stemness	Oncogene	Yao et al., 2015
Pancreatic cancer	Upregulated	miR-34a-5p	Unknown	↑ Cell proliferation ↑ Migration ↑ Invasion ↓ Apoptosis	Oncogene	Sun et al., 2018a
	Upregulated	miR-133a	EGFR	↑ Cell proliferation ↓ Poor prognosis	Oncogene	Wei et al., 2017
	Upregulated	miR-140/ miR-124	iASPP	↑ Cell cycle progression ↑ Cell proliferation Poor clinicopathological features	Oncogene	Liang et al., 2017
Bladder cancer	Upregulated	miR-200c	Unknown	↑ Cancer stem cells clonality and self-renewal EMT	Oncogene	Xu et al., 2018
	Upregulated	miR-124	AR	↑ Cell proliferation ↑ Invasion ↑ Migration	Oncogene	Xiong et al., 2017

Table 1. Functional characterization of XIST in human cancers (Continued)

Cancer type	XIST expression level	XIST molecular target (s)	Downstream genes	Effect on cancer progression and metastasis	Functional role of XIST (oncogene/ tumor suppressor)	References
Bladder cancer	Upregulated	miR-139-5p	Wnt1	↑ Cell growth ↑ Metastasis Worse patient survival	Oncogene	Hu et al., 2017
Cervical cancer	Upregulated	miR-200a	Fus	↑ Tumor progression ↑ Distant metastasis ↑ Tumor size ↑ FIGO stage	Oncogene	Zhu et al., 2018
Osteosarcoma	Upregulated	miR-195-5p	YAP	↑ Cell proliferation ↑ Invasion ↑ EMT ↑ Tumor growth Poor clinical prognosis	Oncogene	Yang et al., 2018
	Upregulated	miR-320b	RAP2B	↑ Cell proliferation ↑ Invasion	Oncogene	Lv et al., 2018
	Downregulated	miR-21-5p	PDCD4	↓ Cell proliferation ↓ EMT ↓ Invasion ↓ Overall survival	Tumor suppressor	Zhang and Xia, 2017
	Upregulated	EZH2	P21	↑ Cell proliferation ↑ Cell cycle	Oncogene	Xu et al., 2017a
Nasopharynx cancer	Upregulated	miR-491-5p	Notch3	↑ Cell proliferation ↑ Invasion ↑ Tumor growth ↓ Apoptosis	Oncogene	Cheng et al., 2018
	Upregulated	miR-29c	Unknown	↑ Cell proliferation ↑ Radioresistance	Oncogene	Han et al., 2017
	Upregulated	miR-34a-5p	E2F3	↑ Cell growth Poor patient survival	Oncogene	Song et al., 2016

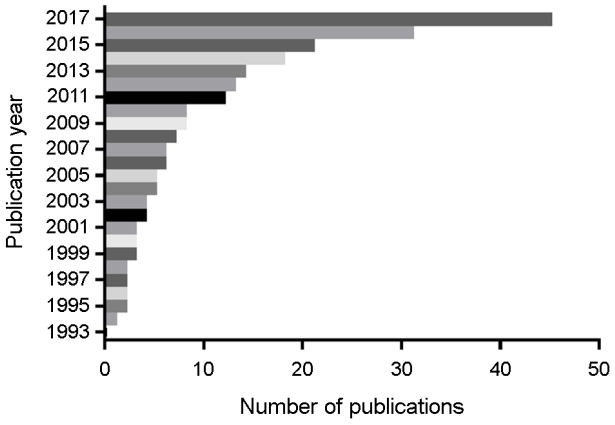

Fig. 1. Change in the number of publications describing the cancer-associated role of XIST. Online analysis from the National Library of Medicine PubMed search using the terms "XIST" and "cancer" (from Jan. 1 to Dec. 31 as date limitations).

in lung carcinogenesis because it was reported to act as a ceRNA on various miRNAs. For instance, in non-small cell lung carcinoma (NSCLC), a thorough analysis of XIST expression revealed that XIST is overexpressed in non-small cell lung cancer tissues compared to normal tissues. In addition, the high expression of XIST in lung cancer tissues and cell lines has been associated with more advanced cancer stages and a worse prognosis. Currently, many studies point to an essential role of XIST in promoting epithelial-mesenchymal transition (EMT), as reported by (Li et al., 2018). In their study, XIST knockdown was sufficient to inhibit ZEB2 expression and to abrogate the TGF-β1-induced EMT in NSCLC, which translates into pulmonary metastasis inhibition in mice mainly by sponging both miR-367 and

miR-141. In support of these findings, Jiang et al. (2018) have shown that XIST overexpression promotes NSCLC invasion by sponging miR-137 *in vitro* and promotes tumor growth *in vivo* as a result of PXN upregulation, a focal adhesion-associated protein that boosts cell migration and mobility. Consistently, the knockdown of XIST suppresses cell proliferation and TGF-β1-induced EMT in NSCLC by sponging miR-137, which induces an aberrant activation of Notch (Wang et al., 2018). In line with the above findings, the modulation of miR-186-5p by XIST boosts lung cancer cell proliferation and invasion (Wang et al., 2017a). On the other hand, Zhang et al. (2017) successfully identified that XIST is a negative regulator of Bcl-2 through reciprocal repression between it and miR-449a. Moreover, a trend for the increased oncogenic expression of XIST has been observed in NSCLC. Consequently, Xu et al. (2017b) showed that the expression of miR-374a was abolished by XIST acting as ceRNA, which was found to be the reason for the upregulation of LARP1, an RNA-binding protein that controls the 5'-terminal oligopyrimidine tract (TOP) mRNA translation as a key regulator of the mTOR pathway. In addition, XIST has been shown to be involved in the epigenetic regulation in NSCLC by interacting with histone modifier such as Enhancer of zeste homolog 2 (EZH2) to suppress the transcription of the KLF2 gene by enhancing its binding to the KLF2 promoter (Fang et al., 2016). Notably, the strong involvement of XIST in autophagy has been demonstrated by Sun et al. (2017b), as XIST knockdown sensitized NSCLC cells to chemotherapy by upregulating miR-17, which targets the 3'-untranslated region of ATG7. Concomitantly, the lncRNA XIST bolsters the resistance of human lung adenocarcinoma cells to cisplatin by functioning as a ceRNA to suppress let-7i, which promotes its downstream target BAG-1, an anti-apoptotic protein shown to interact with BCL-2 (Sun et al., 2017a). In agreement with the above findings, XIST targets miR-140, which blocks iASPP oncogene expression in human lung cancer (Tang et al., 2017).

Colorectal and Gastric cancer

Several recently published studies have examined the alterations affecting XIST in colon cancer. Notably, the interaction of XIST with several miRNAs has been emphasized in colorectal and gastric cancer. For instance, XIST has been reported to be a miR-185 sponge that regulates TGF-β1. Hence, XIST seems to play an oncogenic role in gastric cancer as demonstrated by Zhang et al. (2018). Moreover, according to a study conducted by Sun et al. (2018a), XIST sponged miRNA-34a. The endogenous suppressive effect of XIST promoted the proliferation and invasion of colon cancer cells by Wnt/β-catenin signaling activation, which leads to the upregulation of c-Myc and cyclin D1 (Sun et al., 2018b). On the other hand, XIST has been shown to boost EZH2 by targeting the miR-137-EZH2 axis to foster the tumor metastasis of colorectal cancer cells (Liu et al., 2018a). Consistent with these results, the lncRNA XIST has been proposed as a novel predictive marker for patients with digestive system tumors, as the high expression of XIST was linked with unfavorable overall survival and a poor prognosis (Liu et al., 2018b). In addition, Ma et al. (2017b) have highlighted the cell cycle regulatory role of XIST in gastric cancer where it promotes G1-S cell cycle progression, which has an anti-apoptotic effect and a growth-boosting effect. This effect is mediated through sponging the miR-497 that suppress its downstream target, metastasis-associated in colon cancer 1 (MACC1). Other evidence published by Chen et al. supports previous findings that stipulate that the long non-coding RNA XIST regulates EMT and metastasis in colorectal cancer, as the knockdown of XIST significantly upregulated the expression of miR-200b-3p that targets E-box-binding homeobox 1 (ZEB1), which has a contributing role in metastasis and cancer invasiveness (Chen et al., 2017). These findings are concordant with those of Song et al. (2017) that stipulate that miR-132-3p is sponged by XIST, which is a direct target of Mitogen-Activated Protein Kinase 1 (MAPK1), which promotes colorectal cancer (CRC) survival and proliferation. It should be noted that XIST promotes resistance to chemoresistance drugs such as 5-fluorouracil (5-FU) in colorectal cancer by promoting thymidylate synthase, a crucial enzyme in the early stages of DNA synthesis and a direct target of 5-FU (Xiao et al., 2017). It was also revealed by Chen et al. (2016) that XIST modulates EZH2 expression by sponging miR-101, a negative regulator of EZH2.

Liver cancer

In contrast to what has been observed in lung cancer and gastric cancer, in which the lncRNA XIST serves as an oncogene, the findings on XIST and liver cancer are seemingly conflicting. Hence, additional studies are urgently needed to reconcile these conflicting findings. For instance, Kong et al. (2018) have shown that the aberrant overexpression of XIST in hepatocellular carcinoma cells promoted the proliferation and invasion of liver cancer cells, where XIST might act as a sponge of miR-194-5p, which derepresses MAPK1. However, Chang et al. (2017) reported that the induced overexpression of XIST in hepatocellular carcinoma (HCC) cells abrogates invasion, migration, and proliferation compared to those in control cells. This effect is facilitated through the XIST-mediated epigenetic regulation of miR-181a, a well-known inhibitor of phosphatase and tensin homolog (PTEN). In keeping with this previous finding, Mo et al. (2017) have found a negative correlation between XIST and miR-139-5p and revealed that the reciprocal inhibition between miR-139-5p and XIST promoted pyruvate dehydrogenase kinase 1 (PDK1), a direct target of miR-139-5p and an AKT activator at T308 residue. Consistent with the findings of the Mo et al. (2017) and Ma et al. (2017a) reported that XIST and its activator JPX lncRNA were downregulated in patients with HCC and that JPX/XIST upregulation in patients with hepatocellular carcinoma is associated with a good prognosis. In addition, Zhuang et al. (2016) have just confirmed the aforementioned findings by claiming that miR-92b, a microRNA with an oncogenic role in hepatocellular carcinoma, is targeted by XIST, thus hampering the miR-92a inhibiting effect on Smad7, a TGF-β type 1 receptor antagonist with a tumor suppressor role.

Breast cancer

Zheng et al. (2018) have shown that XIST is a cell growth and metastasis inhibitor in breast cancer. This role seems irrevocably linked to its sponge activity of miR-155, which directly targets CDX1, an inducer of genes related to cell adhesions in angiogenesis and EMT. Of particular interest, a study conducted by Huang et al. (2016) showed that a significant XIST reduction in breast tumor samples and breast cancer cell lines was associated with JPX downregulation and aberrant AKT activation. Moreover, XIST knockdown diminished PHLPP1 expression, which plays an AKT phosphatase role. On the other hand, as the development of resistance to chemotherapy remains an issue in breast cancer as well as many other cancers, Schouten et al. (2016) investigated the impact of XIST and tumor suppressor p53-binding protein 1 (53BP1) expression on recurrence-free survival, disease-free survival, and overall survival in patients with breast cancer carrying the BRCA1 mutation and showed that low 53BP1 and high XIST expression are linked to a poor outcome following high-dose alkylating chemotherapy.

Glioma

Recently published data provide evidence of the oncogenic role of XIST in human glioma, whereby XIST has oncogenic activity by targeting miR-137, based on the findings of Wang et al. (2017b). Indeed, XIST, by sponging miR-137, enhanced Rac1 expression, a pleiotropic regulator of many cellular processes such as the cell cycle, differentiation, invasion, and motility. Notably, in the case of high-grade glioma whereby the use of a combination of chemotherapy and radiotherapy results in a clear improvement, although it remains limited because of recurrence, XIST has been shown to boost the chemoresistance of glioma cells to temozolomide (TMZ) by direct binding to miR-29c. This was confirmed by knockdown of XIST, which significantly increased miR-29c expression but suppressed the expression of MGMT, SP1, and MSH6, which are considered important DNA mismatch repair (MMR) regulators (Du et al., 2017). On the other hand, a causal relationship between XIST expression and glioma angiogenesis and blood-tumor barrier permeability has been established by Yu et al. (2017), who demonstrated that miR-137 is a direct target of XIST, which inhibits FOXC1 and tight junction protein ZO-2 in normal cells. Hence, XIST knockdown facilitates the delivery of chemotherapeutic agents through the blood-tumor barrier and abrogates angiogenesis by reducing the promoter activity of CXCR7. Alternatively, the sponging effect exerted by XIST on miR-429 has been proposed by Cheng et al. (2017) as a promoter of glioma angiogenesis and tumorigenicity. In line with the above findings, Yao et al. (2015) have elucidated the cor-

relation between XIST expression and human glioblastoma stem cells by demonstrating the existence of reciprocal repression between miR-152 and XIST, which bind to each other. Indeed, XIST knockdown promoted the expression of miR-152, which triggered apoptosis and hindered glioma stem cell proliferation, migration, and invasion as well.

Pancreas cancer

Current studies on XIST and pancreas cancer have unanimously agreed that XIST exerts an oncogenic function in pancreatic cancer. It is believed that the knockdown of XIST in pancreatic cancer cells induces apoptosis, reduces proliferation, and inhibits migration and invasion, as supported by the findings of Sun et al. (2018a) whereby the complementary base pairing between XIST and miR-34a-5p, a well-known tumor suppressor, hampered its expression. Therefore, promotes pancreatic cancer progression. In support of this conclusion, Wei et al. (2017) investigated the correlation between XIST and miR 133a and found out that XIST negatively regulated miR-133a and that miR-133a downregulation imposed by XIST boosted EGFR expression as a result of liberating the EGFR 3'-UTR micro-RNA response elements. Moreover, XIST has been reported to act as a promoter of human pancreatic carcinoma by targeting miR-140 and miR-124m, which both target endogenous iASPP and CDK1, two important anti-apoptotic proteins (Liang et al., 2017).

Bladder cancer

Current studies on lncRNA XIST suggest that XIST has an oncogenic role in bladder cancer. While several reports have demonstrated the overexpression of XIST in human bladder tissues, which correlated with a poor prognosis, a recent study by Xu et al. (2018) points to a link between XIST expression and stemness, as the knockdown of XIST in bladder cancer cells dramatically abrogated self-renewal and clone formation efficiency. This effect seems to be mediated through inhibiting miR-200c which is a tumor suppressor that suppresses growth and EMT in bladder carcinoma (Xu et al., 2018). In keeping with these findings, Xiong et al. (2017) have confirmed the interaction between XIST and miR-124. Mechanistically, the interaction between XIST and miR-124 abrogated the binding capability of miR-124 to the androgen receptor (AR) 3'-UTR region and thus promoted AR expression, which boosts bladder cancer progression. In conjunction with previous findings, Hu et al. (2017) provided support for the XIST lncRNA sponge hypothesis, as they concluded that XIST knockdown substantially inhibited bladder cancer growth and metastatic potential *in vitro* and tumor size *in vivo* considering that miR-139-5p targets Wnt1, a proto-oncogene implicated in oncogenesis, embryogenesis, and cell fate determination.

Cervical cancer

In cervical after cancer, the increased expression of XIST has been associated with a better overall survival (OS) in patients with cervical squamous cell carcinoma receiving chemoradiation therapy, as the 4-year overall survival rate was 87.1% in patients highly expressing XIST as opposed to 54.4% in patients with low XIST expression as reported by Kobayashi et al. (2016). In an attempt to investigate the sponge function of XIST in cervical cancer, Zhu et al. (2018) carried out a loss-of-function assay to determine which miRNA is the interaction partner of XIST. Interestingly, miR-200 was inhibited by XIST, which induced the upregulation of RNA-binding protein Fused in Sarcoma/Translocated in Sarcoma (FUS/TLS), an important oncogenic protein.

Osteosarcoma

There is an urgent need to unravel the function of XIST in osteosarcoma. Yang et al. (2018) examined the hypothesis that XIST is a miRNA sponging lncRNA in osteogenic sarcoma by analyzing the interaction of XIST with its downstream target miR-195-5p using dual-luciferase assays and bioinformatics prediction tools. Importantly, XIST was found to be a direct inhibitor of miR-195p, which decreased the binding between the YAP 3'-UTR and miR-195-5p. Hence, the YAP promoter was activated, boosting YAP expression in osteosarcoma cells. Another study conducted by Li et al. (2017) highlighted that XIST overexpression in osteosarcoma has a correlation with advanced tumor size, advanced clinical stage, distant metastasis progression, and thus a poor prognosis in patients with osteosarcoma. Additionally, XIST overexpression promoted osteosarcoma cell proliferation.

In parallel, another interesting finding by Lv et al. (2018) suggested that XIST targeted miR-320b, thus promoting osteosarcoma proliferation and invasion by upregulating ras-related protein RAP2B. On the contrary, XIST has been reported by Zhang and Xia (2017) to play a tumor suppressor role in osteosarcoma by endogenously competing with miR-21-5p, thus upregulating PDCD4, an apoptosis-inducing protein. On another note, Xu et al. (2017a) have reported that XIST overexpression in OS tissues impedes p21 expression epigenetically. This is mediated by XIST binding to EZH2, the main member of the PRC2 complex.

Nasopharyngeal cancer

As detailed in this review, many studies have shown that XIST is an endogenous competitor of several tumor suppressor miRNAs in various tumors, which promotes tumor proliferation, resistance, and metastasis. Nasopharyngeal carcinoma is no exception, as the knockdown of XIST mitigated nasopharyngeal carcinoma advancement by upregulating miR-491-5p, which suppressed Notch3 expression in nasopharyngeal carcinoma cells (Cheng et al., 2018). Moreover, Han et al. (2017) elucidated that miR-29c downregulation by XIST enhanced the radioresistance of nasopharyngeal carcinoma cells, thus demonstrating that the XIST/miR-29c axis might be promising for overcoming nasopharyngeal carcinoma resistance to radiotherapy. Song et al. (2016) clarified the oncogenic function of XIST in nasopharyngeal carcinoma by showing the involvement of XIST in upregulating E2F3 through miR-34a-5p sponging.

CONCLUSION

As it has been almost three decades since the discovery of XIST, the oncogenic role of XIST is systematically being clarified. There is a substantive evidence pertaining to the oncogenic overexpression of XIST across several tumor tissues in conjunction with its ceRNA function, which involves a plethora of miRNA targets that differ in a tissue- and context-dependent manner. Within this framework, significant progress has been achieved in identifying the interacting partners of XIST miRNA *in vitro* and *in vivo*. However, further studies in other cancer types such as leukemia are urgently needed, and several questions that are essential to understand the oncogenic functions of XIST remain unanswered, and thus could open new research avenues.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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