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EDITED BY
Hernandes F. Carvalho,
State University of Campinas, Brazil

REVIEWED BY
Juan Li,
Zhengzhou University, China
Giovanni Blandino,
Hospital Physiotherapy Institutes (IRCCS), Italy

*CORRESPONDENCE
Dajin Chen
zju2001@zju.edu.cn

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The emerging potentials of lncRNA DRAIC in human cancers

Qinfan Yao[1,2,3,4], Xiuyuan Zhang[1,2,3,4] and Dajin Chen[1,2,3,4]*

[1]Kidney Disease Center, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China, [2]Key Laboratory of Kidney Disease Prevention and Control Technology, Hangzhou, China, [3]National Key Clinical Department of Kidney Diseases, Institute of Nephrology, Zhejiang University, Hangzhou, China, [4]Zhejiang Clinical Research Center of Kidney and Urinary System Disease, Hangzhou, China

Long non-coding RNA (lncRNA) is a subtype of noncoding RNA that has more than 200 nucleotides. Numerous studies have confirmed that lncRNA is relevant during multiple biological processes through the regulation of various genes, thus affecting disease progression. The lncRNA DRAIC, a newly discovered lncRNA, has been found to be abnormally expressed in a variety of diseases, particularly cancer. Indeed, the dysregulation of DRAIC expression is closely related to clinicopathological features. It was also reported that DRAIC is key to biological functions such as cell proliferation, autophagy, migration, and invasion. Furthermore, DRAIC is of great clinical significance in human disease. In this review, we discuss the expression signature, clinical characteristics, biological functions, relevant mechanisms, and potential clinical applications of DRAIC in several human diseases.

KEYWORDS

DRAIC, lncRNA, biological function, mechanism, application

Introduction

Long non-coding RNA (lncRNA) is a type of non-protein-coding RNA that is longer than 200 nucleotides (1–5). With the advancement of genomics technology during the past few decades, several lncRNAs have become the focus of clinical research and were

discovered to be closely associated with the progression of human diseases (5–8). There is growing evidence that lncRNA can actively participate in the regulation of a variety of biological functions mainly through the modification of gene expression levels (9–13). These functions include cell proliferation, apoptosis, autophagy, metabolism, invasion, and migration.

The lncRNA DRAIC (Downregulated RNA In Cancer) is a 1.7 kb lncRNA located on the human chromosome 15q23 (14). lncRNA DRAIC was first discovered to act as a tumor suppressor in prostate cancer, but it appears to exert varied biological activity in different diseases. Increasing evidence has indicated that an imbalance in lncRNA DRAIC expression is involved in many diseases especially cancers, including prostate cancer (14–18), lung cancer (19–21), glioma (22–24), breast cancer (25–27), colorectal cancer (28), esophageal cancer (29), gastric cancer (30), nasopharyngeal carcinoma (31), retinoblastoma (32), in addition to Hirschsprung's disease (33, 34) and omphalocele (35). Abnormal expression levels of DRAIC have also been associated with clinicopathological features of patients, such as lymph node metastasis, neoplasm stage, overall survival and progression-free survival. More notably, lncRNA DRAIC exhibited a vital influence on the modulation of abnormal cellular processes and tumorigenesis progression through cell proliferation, invasion, migration, and autophagy. Mechanistic investigations have further prompted major advances in the clinical applications of lncRNA DRAIC, including its potential for diagnosis, prognosis, and treatment. In this review, we first focus on the biological functions, relevant mechanisms, and future clinical applications of lncRNA DRAIC, and summarize available knowledge on the expression profiles and clinical characteristics of lncRNA DRAIC in disease processes.

The role of the lncrna draic in cancers

LncRNA DRAIC was shown to be aberrantly expressed in several types of human disease, including prostate cancer, lung cancer, glioma, breast cancer, colorectal cancer, esophageal cancer,

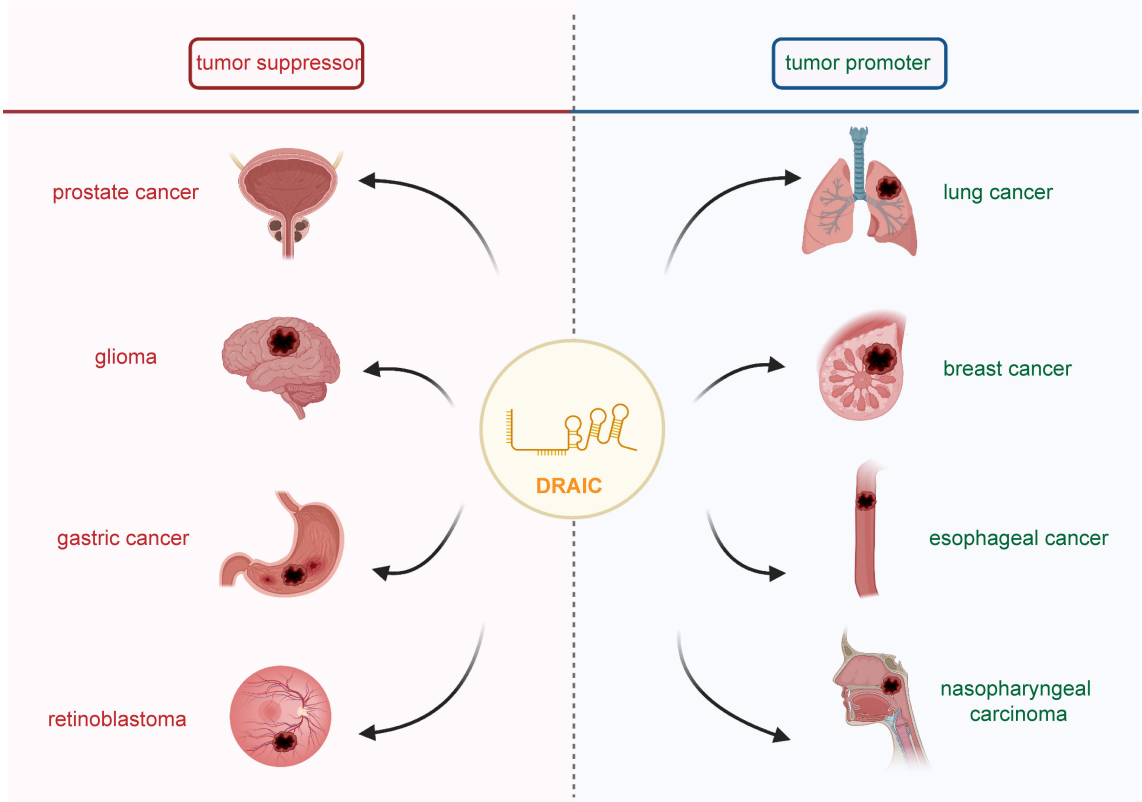

FIGURE 1
The role of lncRNA DRAIC in human cancers. It has been shown that lncRNA DRAIC acts as a tumor suppressor in prostate cancer, glioma, gastric cancer, and retinoblastoma. DRAIC also functioned as an oncogene in lung cancer, breast cancer, esophageal cancer and nasopharyngeal carcinoma.

TABLE 1 lncRNA DRAIC expression and clinical characteristics in human diseases.

Disease type	Expression	Clinical characteristics	Refs
prostate cancer	downregulated	overall survival, and disease-free survival	33430890,31900260, 28241429,27562825,25700553
lung cancer	upregulated	TNM stage, lymph node metastasis, and poor prognosis	34764698,34306024,33771173
glioma	downregulated	overall survival, and progression-free survival	34746949,33767991,33336743
breast cancer	upregulated	overall survival, and disease specific survival	34645975,30872794,30544991
esophageal cancer	upregulated	/	32659236
gastric cancer	downregulated	lymph node metastasis	32351584
nasopharyngeal carcinoma	upregulated	advanced clinical stage	31497998
retinoblastoma	downregulated	/	31058073
Hirschsprung's disease	upregulated	/	34471485,31647312
Omphalocele	downregulated	/	30538881

gastric cancer, nasopharyngeal carcinoma, retinoblastoma, Hirschsprung's disease, and omphalocele (Figure 1). Indeed, lncRNA DRAIC expression was shown to have a significant association with patient clinicopathological features (Table 1). LncRNA DRAIC also exerts key roles in multiple cellular processes *via* diverse mechanisms (Table 2).

The tumor-suppressor role of DRAIC in cancers

Prostate cancer

Prostate cancer (PCa) is the most frequent malignant tumor and accounts for the second leading cause of cancer-related deaths in men (36–40). The androgen receptor (AR) plays a crucial role in the pathogenesis of PCa and is considered a clinically validated target for the treatment of PCa (41–44). Unfortunately, long-term androgen deprivation can ultimately lead to castration-resistant PCa (CRPC), which favors metastasis and poor prognosis (45–47). Although much effort has been made to improve PCa treatment, it is still needed to identify more sensitive biomarkers to guide early diagnosis and treatment (37, 48, 49). Several studies have shown that lncRNA DRAIC is dysregulated in PCa LNCaP and C4-2B cells as well as in 7 PCa tumor biopsies by androgens in a dose and time-dependent manner (14–18). Moreover, lncRNA DRAIC was considered to be a tumor suppressor by preventing the transformation of cuboidal epithelial cells to fibroblast-like morphology as well as cell migration and invasion. *In vivo*, lncRNA prevents the growth of xenograft tumors.

Glioma

Glioma is one of the most prevalent primary malignant tumors in the central nervous system, accounting for about 81%

TABLE 2 Functions and mechanisms of lncRNA DRAIC in cancers.

Disease type	Cell lines	Functions	Related mechanisms	Refs
prostate cancer	LNCaP, and C4-2B cells	cell migration, and invasion	FOXA1, NKX3-1, IKK, and NF-κB	33430890,31900260, 28241429,27562825, 25700553
lung cancer	Calu-3, HCC827, NCI-H441, and NCI-H1975 cells	cell proliferation, migration, and invasion	miR-3940-3p	34764698,34306024, 33771173
glioma	U251, A172, U87, and U373 cells	cell proliferation, migration, invasion, and autophagy	AMPK, NF-κB, mTOR, S6K1, H3K4me3, SET7/9, and miR-18a-3p	34746949,33767991, 33336743
breast cancer	HeLa, T47D, MCF-7, SKBR3, MDA-MB-361, and MDA-MB-231 cells	cell proliferation, migration, invasion, autophagy, and apoptosis	FOXP3, miR-432-5p, and SLBP	34645975,30872794, 30544991
esophageal cancer	Eca-109, TE-1, EC9706, and OE19 cells	cell proliferation, invasion, apoptosis, and autophagy	miR-149-5p, and NFIB	32659236
gastric cancer	HGC-27, SGC-7901, BGC-823, AGS, and MKN45 cells	cell proliferation, migration, and invasion	UCHL5, and NFRKB	32351584
nasopharyngeal carcinoma	CNE-1, and C666-1 cells	cell proliferation, migration, and invasion	miR-122, and SATB1	31497998
retinoblastoma	Y79 cells	cell proliferation	/	31058073

of malignant brain tumors (50–52). lncRNA DRAIC has been shown to be downregulated in glioma tissues and cell lines (U251, A172, U87, and U373 cells) (22–24). Survival analysis has indicated that a high lncRNA DRAIC expression was associated with a remarkably favorable overall survival and progression-free survival of lower-grade glioma patients who had been submitted to radiotherapy (23). lncRNA DRAIC repressed cell proliferation, migration, invasion, and *in vivo* xenograft tumor growth, as well as induced cell autophagy in U251, A172, and U87 cells (22, 24).

Gastric cancer

Gastric cancer is one of the most frequent digestive tract cancers, which accounts for a large proportion of cancer-related morbidity and mortality worldwide (53–57). Although advances have been made in the treatment of patients with gastric cancer over the past few years, their 5-year survival rate is still lower than 25% (58–61). Of note, novel biomarkers should be identified to improve the early diagnosis and survival rates of gastric cancer patients (61–63). The expression of lncRNA DRAIC was downregulated according to tumor progression in 67 primary gastric cancer patients who were submitted to surgical resection as well as in HGC-27, SGC-7901, BGC-823, AGS and MKN45 cell lines (30). A high lncRNA DRAIC level was significantly associated with lymph node metastasis, while the downregulation of DRAIC inhibited cell proliferation and metastasis in HGC-27, MKN45, and SGC-7901 cells.

Pediatric retinoblastoma

Retinoblastoma is the most common intraocular tumor in children and is initiated by the biallelic inactivation of the retinoblastoma 1 (RB1) gene (64–68). A recent a study revealed that lncRNA DRAIC was dysregulated in retinoblastoma Y79 cells and 7 retinoblastoma tissues. This lncRNA was involved in the modulation of Y79 cell growth and proliferation (32).

The tumor-promoting role of DRAIC in cancers

Lung cancer

Lung cancer is the most commonly diagnosed malignancy worldwide and lung adenocarcinoma (LUAD) represents the most common histological type of lung cancer (69–73). A late diagnosis of LUAD contributes to high metastasis and mortality rates, emphasizing the urgency for better identification of sensitive biomarkers during lung cancer progression (69, 74–76). High expression of lncRNA DRAIC was recently observed in LUAD tissues and cell lines (Calu-3, HCC827, NCI-H441, and NCI-H1975 cells) and was positively correlated with TNM stage, lymph node metastasis, and a poor prognosis (19–21). lncRNA DRAIC has been proved to exhibit tumorigenic effects through the regulation of cell proliferation, migration, and invasion of Calu-3 and HCC827 cells.

Breast cancer

Breast cancer is a common malignancy with high incidence and morbidity rates in females (77–81). Therefore, establishing an effective biomarker is essential to decrease mortality and improve the survival rate for breast cancer patients (81–84). lncRNA DRAIC expression was distinctly upregulated in 828 breast cancer specimens and cell lines (HeLa, T47D, MCF-7, SKBR3, MDA-MB-361, and MDA-MB-231 cells). Kaplan–Meier plots and log-rank tests have shown that a high expression of lncRNA DRAIC was correlated with a poorer overall survival and disease specific survival, especially in ER-positive breast cancer patients (27). In addition, lncRNA DRAIC stimulated tumor progression through the promotion of cell proliferation, migration, and invasion, as well as the inhibition of cell autophagy and apoptosis in SKBR3, MCF-7 and MDA-MB-231 cells (25, 26).

Esophageal cancer

Esophageal cancer is a common upper gastrointestinal malignancy that ranks eighth in the world among cancer incidence, especially in China (85–89). High levels of DRAIC were found in esophageal cancer cells Eca-109, TE-1, EC9706, and OE19 (29). Moreover, DRAIC played an oncogene role since it facilitated cell proliferation and invasion, and repressed cell apoptosis and autophagy in Eca-109 and EC9706 cells.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma is an epithelial carcinoma generated within the nasopharyngeal mucosal lining (90–94). lncRNA DRAIC was highly expressed in nasopharyngeal carcinoma cell lines CNE-1 and C666-1 as well as in 32 biopsy tissues (31). Moreover, a high expression level of lncRNA DRAIC showed a close relationship with higher clinical stages. In addition, lncRNA DRAIC acted as an oncogene and enhanced cell proliferation, migration and invasion in CNE-1 and C666-1 cells.

Accumulating evidence has reported that the differential expression of DRAIC in prostate cancer, lung cancer, glioma, breast cancer, colorectal cancer, esophageal cancer, gastric

cancer, nasopharyngeal carcinoma, and retinoblastoma. And its abnormal expression was significantly related to many clinicopathological features, notably the patient's prognosis. Furthermore, DRAIC was implicated as a regulator of a wide variety of cellular processes and then participated in the pathogenesis and progression of numerous human disorders. Therefore, elucidating the underlying molecular mechanisms of DRAIC in cancer progression has been proven to hold promise to support its clinical application significance.

Regulatory mechanisms of lncrana draic

Several studies have reported that lncRNA DRAIC actively participates in crucial biological processes of many diseases, such as cell proliferation, apoptosis, autophagy, invasion and migration. Here, we discuss the main biological functions and molecular mechanisms of lncRNA DRAIC during disease progression.

Cell proliferation

It is well known that cells proliferate excessively which ultimately results in tumor progression (95–98). In glioma, lncRNA DRAIC has been demonstrated to suppress the proliferation of U251 cells by targeting miR-18a-3p (24). And lncRNA DRAIC was activated by FOXP3 in breast cancer and promoted cell proliferation in SKBR3 and MDA-MB-231 cells *via* sponging miR-432-5p to increase SLBP levels (25). lncRNA DRAIC was also found to improve MCF-7 cell proliferation in an autophagy-independent manner by regulating the activity of ULK1 and enhancing LC3B expression (26). Similarly, lncRNA DRAIC led to cell proliferation in esophageal cancer Eca-109 and EC9706 cells through the miR-149-5p/NFIB axis (29). In gastric cancer, lncRNA DRAIC has also been indicated to inhibit the proliferation of SGC-7901, HGC-27, and MKN45 cells by binding to UCHL5 and accelerating the ubiquitination of NFRKB (30). Additionally, lncRNA DRAIC increased the proliferation of nasopharyngeal carcinoma CNE-1 and C666-1 cells *via* an interaction with miR-122 and up-regulation of SATB1 (31).

Cell migration and invasion

Metastasis, also termed invasion-migration cascade, is a multistep process that involves the dissemination of tumor cells from the primary tumor site to distant organs and subsequent formation of secondary tumors (99–103). As the major reason behind most cancer-related deaths, metastasis is a current challenge to improve the survival of cancer patients (99, 104–107).

DRAIC was shown to positively regulate FOXA1 and NKX3-1 and to block the transformation of LNCaP prostate cancer cuboidal epithelial cells to a fibroblast-like morphology. This subsequently hindered cell migration and invasion through an interaction with IKK that inactivated NF-κB (Figure 2) (14, 16). In glioma cells, lncRNA DRAIC also exerted pro-migratory and invasive roles *via* the repression of NF-κB, coupled with increases in AMPK phosphorylation and thus inhibition of mTOR activity and phosphorylation of key substrates like S6K1 (22). Moreover, the interaction between the H3K4me3 protein and the lncRNA DRAIC promoter was mediated by SET7/9 and increased the association of DRAIC with miR-18a-3p. These mechanisms were shown to improve the metastasis of U251 cells (24). And in breast cancer cell lines, lncRNA DRAIC was up-regulated by FOXP3 and promoted cell migration and invasion *via* the miR-432-5p/SLBP axis (25).Moreover, lncRNA DRAIC improved esophageal cancer Eca-109 and EC9706 cell invasion through binding to miR-149-5p, which regulated NFIB levels (29). lncRNA DRAIC also hindered cell metastasis through its interaction with UCHL5 and repression of NFRKB deubiquitination in gastric cancer (30). In nasopharyngeal carcinoma cells, lncRNA DRAIC boosted cell migration and invasion through its interaction with miR-122 and the consequent increase of SATB1 levels (31). Furthermore, lncRNA DRAIC facilitated the migration of HSCR 293T and SH-SY5Y cells by sponging miR-34a-5p, which positively modulated ITGA6 expression (33).

Cell autophagy

Autophagy is a process of intracellular component degradation that maintains cellular homeostasis (26, 108–111). Its dysfunction contributes to a series of pathophysiological processes of various diseases, including cancer. Studies have identified that numerous lncRNAs regulate autophagy through various mechanisms (112–115). lncRNA DRAIC has been reported modeulate autophagy in glioblastoma A172 and U87 cells by downregulating the NF-κB target gene GLUT1, increasing AMPK levels, and thus inhibiting mTOR (22, 116). lncRNA DRAIC also suppressed cell autophagy in breast cancer MCF-7 cells through the activation of ULK1 (26). Similarly, lncRNA DRAIC was found to inhibit cell autophagy in esophageal cancer Eca-109 and EC9706 cells acting as ceRNAs to modulate the expression of NFIB by quenching miR-149-5p (Figure 3) (29). Take together, DRAIC was involved in the multiple biological process of cancers through interaction with diverse molecules (Figure 4).

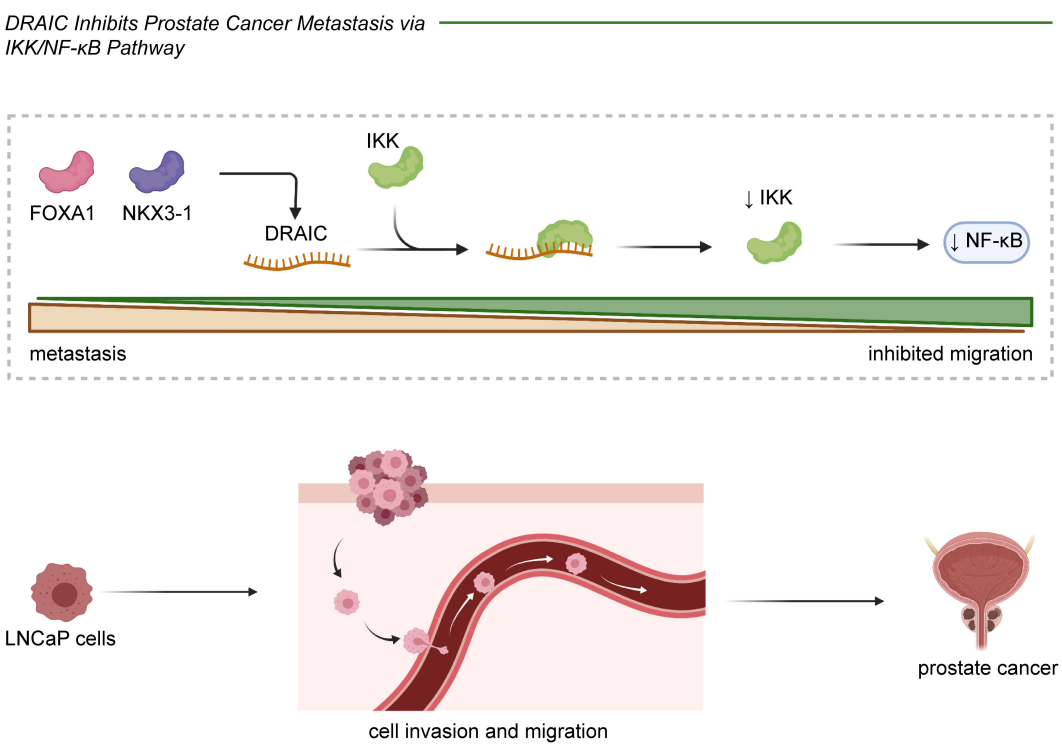

FIGURE 2
In prostate cancer, lncRNA DRAIC played a tumor suppressive role through inhibiting cell migration and invasion. DRAIC was activated by FOXA1 and NKX3-1 and interacts with IKK to further decrease NF-κB expression in LNCaP cells.

Prospects for the clinical applications of draic in disease management

In recent years, numerous studies have shown the significance of lncRNAs in clinical applications for human disease, especially in cancer (117–121). lncRNA DRAIC is a newly identified lncRNA involved in multiple human diseases. Previous evidence suggests that DRAIC is extensively involved in the modulation of numerous biological functions and intimately associated with pathological characteristics, which may be valuable for clinical diagnosis, prognosis, and treatment. In this section, we address the promising significance of lncRNA DRAIC in human disease.

DRAIC as a diagnostic and prognostic biomarker

The expression levels of lncRNA DRAIC in a diverse array of tissues and cell lines were observed to be differentially regulated depending on the disease state, which reveals that lncRNA DRAIC expression can be used to distinguish between normal and diseased tissues. Therefore, assessing lncRNA DRAIC concentration may effectively act as a method for the early diagnosis of diseases. Besides, increasing data supports that lncRNA DRAIC expression is significantly associated with a variety of clinicopathological features, demonstrating the promising potential for prognosis prediction. For example, lower levels of DRAIC were observed as PCa progressed from AD to CR. This was associated with a lower disease-free-survival rate of patients verified by the Kaplan-Meier plot (14). lncRNA DRAIC was overexpressed at a higher level in high malignancy breast cancers when compared to low malignancy cases, suggesting its diagnostic and prognostic value (27). In low-grade glioma, DRAIC was shown to reflect the prognosis of radiotherapy treatment (27). Additionally, lncRNA DRAIC was perceived as a novel prognosis biomarker for risk evaluation of HSCR (34). In LUAD, lncRNA DRAIC was regarded as an immune-related RNA and incorporated into the 5-lncRNA-based model and 5-lncRNA risk signature, which has been shown to accurately predict the prognosis of patients (20, 21). However, lncRNA DRAIC was mainly measured in cell lines and tissues, which must be optimized to a more accessible and convenient approach. Tissue biopsy has several drawbacks, such

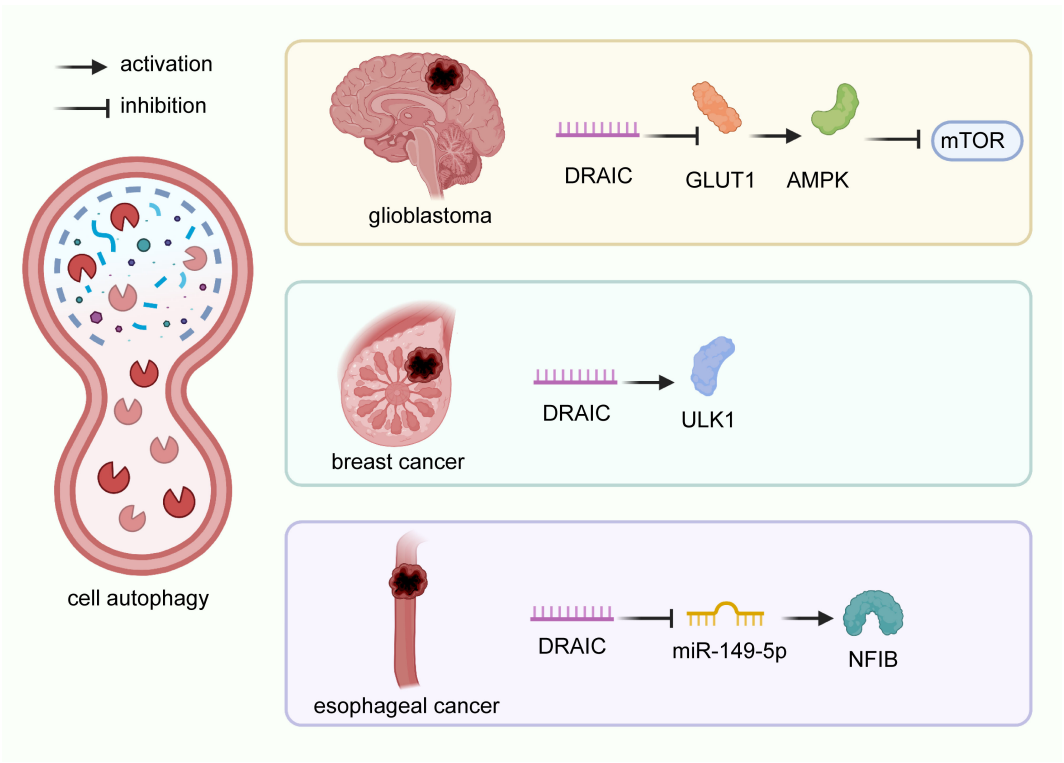

FIGURE 3
Regulatory mechanisms of DRAIC on cell autophagy in cancers. In glioblastoma A172 and U87 cells, lncRNA DRAIC induced autophagy by downregulating the NF-κB target gene GLUT1, which activated AMPK, and blocked the expression of mTOR. In breast cancer MCF-7 cells, DRAIC enhanced ULK1 expression and inhibited cell autophagy. In esophageal cancer, lncRNA DRAIC suppressed cell autophagy through its interaction with miR-149-5p and up-regulation of NFIB.

as invasiveness, complicated manipulation, high cost, bleeding complications, poor reproducibility, and sampling variability. Minimally invasive (e.g., saliva, urine, and blood) detection of lncRNA DRAIC expression and sensitivity is an increasing research interest for its diagnostic and prognostic applications.

LncRNA DRAIC as a treatment target

The abnormal expression of lncRNA DRAIC in disease also provided novel insights for disease treatment. Alterations of lncRNA DRAIC expression may be developed as a therapeutic target for the inhibition of disease progression. Furthermore, the molecular mechanisms through which DRAIC regulates the pathogenesis of diseases also resulted in an effective therapy target. Knockdown or activation of lncRNA DRAIC and relevant molecules, as well as the regulation of intramolecular interactions, may also serve as potential targeting candidates for novel pharmaceutical development and molecular-targeted therapies (122). Indeed, lncRNA DRAIC knockout was confirmed to suppress the tumorigenesis of PCa PC3M cells by inhibiting the NF-κB pathway in nude mice. Moreover, lncRNA DRAIC expression was shown to reflect the sensitivity of tumor cells to chemotherapy or radiotherapy. For example, lncRNA DRAIC expression was demonstrated to predict patient response to radiosensitivity in lower-grade glioma (23). In breast cancer, the expression level of lncRNA DRAIC can reflect the efficacy of chemotherapy drugs, such as paclitaxel, FEC, and lapatinib, which may contribute to guiding more sensitized and individualized treatment options for patients (27). In addition, existing research on DRAIC has mainly been concentrated on the cellular level with a deficiency of *in vivo* studies. lncRNA DRAIC was currently explored in only a small portion of human diseases, and there is little known about the multifaceted role and functional mechanisms of DRAIC in other types of disease. Further *in vivo* experiments are required to determine whether the molecular mechanisms of lncRNA DRAIC on disease progression discovered by *in vitro* studies are consistent. Besides, more mechanistic insights of lncRNA DRAIC in other diseases probably also contribute to the development of better-targeted therapeutics.

In general, lncRNA DRAIC was proved to be a potential diagnostic and prognosis biomarker, together with a treatment target for human cancers. Further investigation is needed to determine the expression profile, sensitivity and stability of

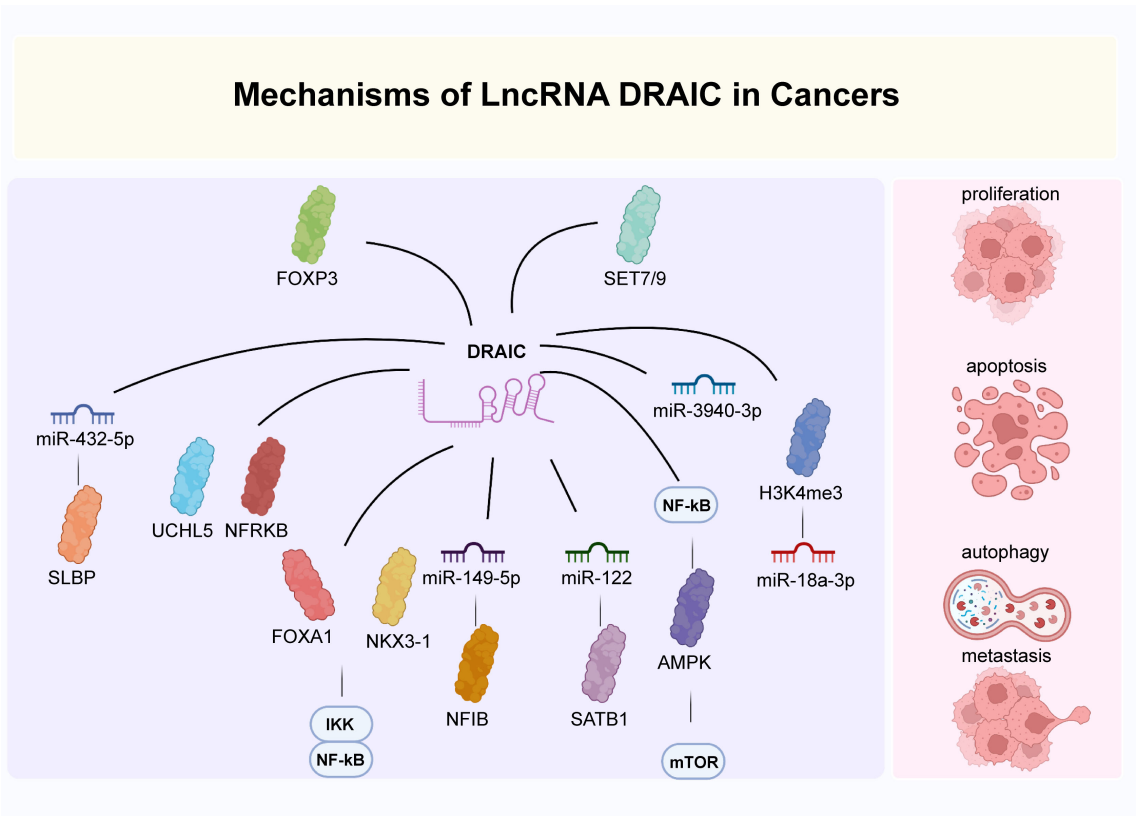

FIGURE 4
The main mechanisms of DRAIC in cancers. DRAIC participated in the regulation of biological processes of cancers through interaction with diverse molecules.

lncRNA DRAIC in non-invasive samples. This could improve disease diagnosis and prognosis as well as the efficiency and safety of lncRNA DRAIC-targeted treatment.

Conclusion

Numerous reports have shown that lncRNA DRAIC is abnormally expressed in PCa, lung cancer, glioma, breast cancer, colorectal cancer, esophageal cancer, gastric cancer, nasopharyngeal carcinoma, retinoblastoma, HSRC, and omphalocele. Moreover, lncRNA DRAIC exhibited a significant association with patient clinicopathological characteristics, especially immune cell infiltration, tumor stage, lymph node metastasis, overall survival and progression-free survival. lncRNA DRAIC was demonstrated to exert momentous roles in multiple cellular process, such as cell proliferation, invasion, migration, and autophagy. Functional assays have revealed a series of molecular mechanisms of lncRNA DRAIC in the development of diseases. These features can be exploited for various medicinal applications, including diagnosis, prognosis and treatment of human diseases.

Extensive research has been undertaken to explore the clinical application of lncRNAs in the past few years (123). The majority of non-invasive biopsy biomarkers are currently being investigated for diagnostic and prognostic purposes (124). The detection of lncRNA DRAIC expression can be used as a promising clinical biomarker for early diagnosis and prognosis. Additional studies are necessary to validate whether lncRNA DRAIC can be detected in non-invasive samples and further verify the stability and specificity of its expression in non-invasive samples. Moreover, lncRNA DRAIC and the relevant molecular pathways may also be applied as new candidates for targeted treatment of several diseases. However, the available studies mainly focus on the expression of lncRNA DRAIC on clinical tissue samples and *in-vitro* cell lines, lacking enough *in vivo* animal studies. The follow-up animal experiments and prospective studies are needed to confirm the efficacy and safety of lncRNA DRAIC-targeted therapy. And the roles and mechanisms of lncRNA DRAIC have merely been explored in a

comparably small number of diseases. It is necessary to further probe the role of lncRNA DRAIC in other disease types.

Author contributions

DC provided a source of ideas for this review. XZ collected the related paper. QY drafted and reviewed the manuscript. All authors have contributed substantially to the original research and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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