REVIEW

Research Progress of Long Non-Coding RNA in Tumor Drug Resistance: A New Paradigm

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Abstract: In the past few decades, chemotherapy has been one of the most effective cancer treatment options. Drug resistance is currently one of the greatest obstacles to effective cancer treatment. Even though drug resistance mechanisms have been extensively investigated, they have not been fully elucidated. Recent genome-wide investigations have revealed the existence of a substantial quantity of long non-coding RNAs (lncRNAs) transcribed from the human genome, which actively participate in numerous biological processes, such as transcription, splicing, epigenetics, the cell cycle, cell differentiation, development, pluripotency, immune micro-environment. The abnormal expression of lncRNA is considered a contributing factor to the drug resistance. Furthermore, drug resistance may be influenced by genetic and epigenetic variations, as well as individual differences in patient treatment response, attributable to polymorphisms in metabolic enzyme genes. This review focuses on the mechanism of lncRNAs resistance to target drugs in the study of tumors with high mortality, aiming to establish a theoretical foundation for targeted therapy.

Keywords: lncRNA, drug resistance, chemotherapy, tumor, immune escape

Introduction

Cancer is one of the leading causes of death worldwide, and the primary treatment options for cancer include chemotherapy, radiotherapy, and surgery. However, several studies have highlighted that, in comparison to surgery or radiotherapy, chemotherapy demonstrates a reduction in tumor recurrence and mortality rates among cancer patients.[1] Despite the recent progress in cancer treatment due to the emergence of targeted therapy and immunotherapy, the presence of both intrinsic and acquired resistance to chemotherapy remains a major factor contributing to cancer-related deaths.[2]

Recent researches have revealed that lncRNA genes constitute a substantial portion of the genomes in complex organisms. These lncRNAs exhibit a faster evolutionary rate compared to protein-coding sequences, displaying cell-type specificity and playing crucial roles in various physiological processes such as cell differentiation and development.[3] Additionally, aberrant expression levels of lncRNAs may closely correlate with the initiation, metastasis, and drug resistance of malignant tumors, thereby influencing the prognosis of cancer patients, including those with lung, liver, gastric, colorectal, and breast cancer, among others. Notably, lncRNAs exhibit limited conservation across species, along with low expression levels and tissue specificity.[4] Extensive study is essential to understand the complex reasons behind drug resistance in cancerous tumors, in order to develop better treatment strategies that can improve patient survival rates.

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gastric, colorectal, and breast cancer, among others. Notably, lncRNAs exhibit limited conservation across species, along with low expression levels and tissue specificity.[4] Extensive study is essential to understand the complex reasons behind drug resistance in cancerous tumors, in order to develop better treatment strategies that can improve patient survival rates.

In this review, we have discussed reports from the past decade, covering various lncRNAs and their roles in regulating the expression of key molecules ranging from epigenetic modifications to post-translational modifications. We provide insights into the regulatory mechanisms of lncRNAs in cancer drug resistance and outline their contributions to the latest advancements in tumor immunotherapy resistance. Notably, our investigation focuses on malignancies with high mortality rates[5] (Table 1), highlighting lncRNAs as potential prognostic and diagnostic biomarkers, as well as clinical targets for cancer treatment, particularly in the context of frontline therapeutic interventions.

Structure and Function of LncRNA

LncRNAs are a class of non-coding RNA molecules over 200 nucleotides that lack open reading frames (ORFs) and lack protein coding capacity. Up to 2% of the human genome encodes for proteins suggesting rest are protein noncoding genes. The current GENCODE database includes17904lncRNAs and 14,739 genes in the human genome, exceeding the number of protein-coding transcripts.[6] This discovery has drawn attention to the roles of lncRNA in cells.

LncRNAs can bind to DNA, RNA, and proteins to regulate gene expression at multiple levels, including transcription, post-transcriptional processing, RNA metabolism, translation, and post-translational modifications.[7] (1) Epigenetic regulation. LncRNAs are essential regulators of epigenetic modifications, such as DNA methylation, histone modification, and chromosome remodeling, which in turn modulate gene expression.[8] For example, the hox transcript antisense RNA (HOTAIR), derived from the HOXC gene, which aids in the recruitment of polycomb repressive complex 2 (PRC2) to specific gene loci, resulting in histone H3 (H3K27) methylation and subsequent downregulation of gene expression.[9] This results in the suppression of genes that help prevent breast cancer from spreading. In prostate cancer patients, C-Terminal binding protein 1 antisense (CTBP1) expression is inhibited by histone deacetylase protein (HAD), induced by the PTB-associated splicing factor (PSF).[10] (2) Transcriptional-level regulation. LncRNA can impact DNA transcription and translation through cis-regulation and transaction, as well as activate transcription factor activity.[11] For instance, linc0255 increases E2 promoter-binding factor 1 (E2F1) translation by interacting with ribosomal protein L35 (RPL35) in MyCN-amplified neuroblastomas, while disrupted in renal carcinoma 3 (DIRC3) affects chromatin structure and enhances transcription of nearby tumor suppressor genes like IGFBP5.[12] (3) Post-transcriptional level regulation. lncRNAs regulate gene expression by binding to mRNA and affecting key processing sites. They can also act as precursors for miRNA, impacting biological functions.[13] For instance, Wang et al observed that the lncRNA Highly Up-regulated in Liver Cancer (HULC) functions as an endogenous miRNA sponge in vivo, sequestering multiple miRNAs and thereby inhibiting their original functions, which ultimately promotes the progression of hepatocellular carcinoma.[14]

Table 1 Distribution of Cases and Deaths for the Top 5 Most Common Cancers in 2020

Cancer Site	Both Sexes Mortality		Male Mortality		Female Mortality	
	No. of New Deaths	% of All Sites	No. of New Deaths	% of All Sites	No. of New Deaths	% of All Sites
All cancers	9,958,133	–	5,528,810	–	4,293,223	
Lung	1,796,144	18.0	1,188,679	21.5	607,465	13.7
Colon	576,858	5.8	515,637	9.3	419,536	9.5
Liver	830,180	8.3	577,522	10.5	252,658	5.7
Stomach	768,793	7.7	502,788	9.1	266,005	6.0
Female breast	684,996	6.9	–	–	684,996	15.5

Note: GLOBOCAN 2020.

In cancer cells, lncRNA dysregulation is prevalent. LncRNAs regulate cell proliferation, apoptosis, invasion, and angiogenesis. Therefore, lncRNAs hold potential as valuable diagnostic, therapeutic, and prognostic markers in cancers.[15]

LncRNA Drug Resistance Mechanisms

lncRNAs are involved in many cellular and genomic processes that regulate the sensitivity of tumor cells to chemotherapeutic agents.[16] Currently, lncRNA regulates chemotherapy drug resistance via the following mechanisms: (1) Drug efflux system alteration. P-glycoprotein (P-gp/ABCB1) is an ATP-binding cassette (ABC) transporter that is implicated in multidrug resistance (MDR) in cancer cells. Additionally, the lncRNA, such as MRP1/ABCC1, MRP2/ABCC2, MRP4/ABCC4, and BCRP/ABCG2, specifically influences ABC transporters, contributing to the development of drug resistance.[17] (2) DNA damage repair and cell cycle regulation. Cell cycle arrest occurs after DNA damage by activating the cell cycle monitoring site pathway or cyclin-dependent kinase. In drug-resistant lung and colon cancer cells, lncRNA MEG3 (maternally expressed gene 3) and SnaR (small NF90-associated RNA) are down-regulated. MEG3 can regulate Cisplatin (DDP) resistance by regulating the expression of P53 and Bcl-XL.[18] LncRNA P21 is an important CDK (the cyclin-dependent kinase) inhibitor in lung adenocarcinomas, inducing cell cycle arrest in response to DNA damage and mediating HOTAIR-induced resistance to cisplatin. Overexpression of HOTAIR (HOX antisense intergenic RNA) leads to downregulation of P21, which further induces drug resistant.[19] (3) Apoptosis. The abnormal regulation of apoptosis may contribute to the proliferation of tumor cells to produce drug resistance. LncRNAs can induce apoptosis resistance in tumor cells by up-regulating pro-survival factors such as Bcl-2, nuclear factor-kappaB (NF-κB) and inhibitor of apoptosis protein (IAP), or inhibits the expression of tumor suppressor genes like caspase and p53, leading to drug resistance.[20] (4) Epithelial mesenchymal Transformation (EMT) and Tumor stem Cell Formation (CSC). After chemotherapy, tumor cells undergo EMT, which leads to secondary drug resistance. Increasing evidence shows that EMT and CSC accumulation are linked to tumor drug resistance, recurrence and metastasis and that lncRNA plays a crucial role in these processes. For example, lncRNA LEIG enhances the sensitivity of gastric cancer cells to 5-Fu by inhibiting the EMT process.[21] In addition, lncRNA GAS5 (growth-arrest-specific 5) inhibits gemcitabine resistance in pancreatic cancer (PAAD) by inhibiting the EMT process and CSC caused by the mi R221/SOCS3 pathway[22] (Figure 1).

LncRNA in Tumorigenesis and Chemotherapy Resistance
Gastric Cancer

Chemotherapy is the main treatment for patients with advanced gastric cancer (GC). First-line treatment drugs include 5-fluorouracil (5-FU), paclitaxel (PTX), platinum drug, etc.[23] Overexpression of lncRNA AK022798 leads to DDP resistance in GC cells via downregulation of caspase-8 and caspase-3 expression.[24] lncRNA UCA1 (urothelial carcinoma-associated 1) as a miR-27b Sponge to down-regulate the expression of caspase-3 and inhibit the exogenous apoptotic pathway in GC cells, resulting in resistance to DDP, Adriamycin (ADR).[25] By significantly increasing lncRNA SNHG5 (small nucleolar RNA host gene 5), the expression of BAX and BCL-2 is downregulated, which inhibits the apoptosis and promotes resistance to DDP of GC cells.[26] lncRNA PVT1 (plasmacytoma variant translocation 1) enhances 5-FU resistance by activating BCL-2, Wang et al found that PVT1 up-regulates HIF-1α (Hypoxia-inducible factor-1alpha) expression and inhibits apoptosis.[27] Furthermore, LncRNA HOTAIR had a significant effect on GC patients and DDP-resistant cells by targeting miR-34a, activating PI3K/AKT, and inhibiting the Wnt/β-catenin pathway, which increased the BAX/BCL-2 ratio, inhibited apoptosis.[28] LINC01433 reduces YAP phosphorylation by disrupting YAP-lats1 binding, while YAP directly binds to the LINC01433 promoter region and activates its translation. The LINC01433-YAP feedback circuit inhibits apoptosis and induces resistance to doxorubicin (DOX) and DDP.[29] Moreover, lncRNA MALAT1/miR-23b-3p increases ATG12 expression, which increases autophagy during gastric cancer treatment with 5-FU, CDDP, and vincristine (VCR).[30] There is significant evidence that lncRNAs play a role in platinum resistance in gastric cancer.

Colorectal Cancer

Colon cancer (CRC) is the second leading cause of death after lung cancer. The first-line chemotherapeutic agents for CRC patients include 5-FU, irinotecan (IRT), oxaliplatin (OXA), and capecitabine.[31]
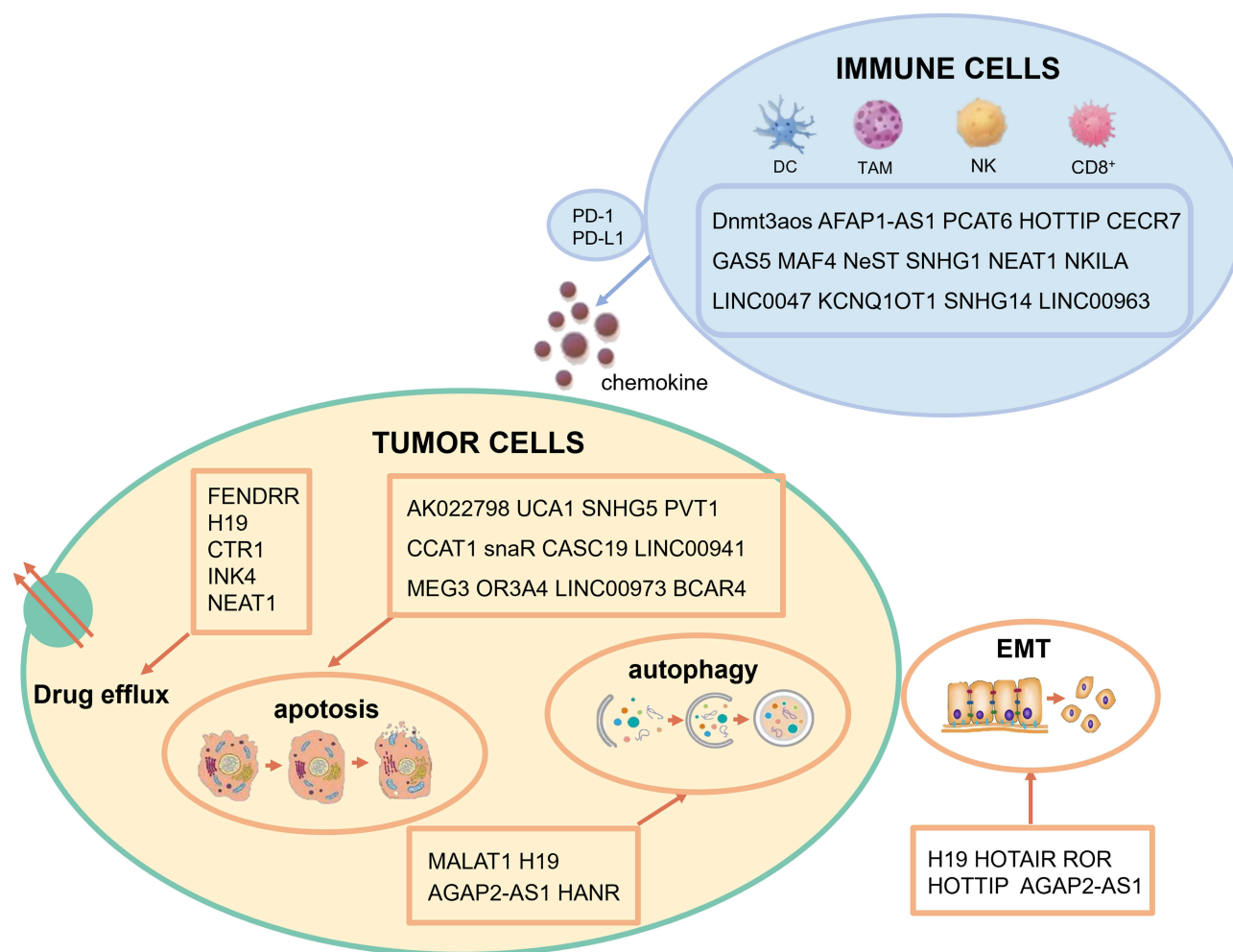
Figure 1 LncRNAs drug resistance mechanisms.

It has been reported that lncRNAs may play a role in drug resistance in cancer. In the GEO database, Li et al[32] analyzed the GSE39582 CRC dataset and discovered 31downregulated lncRNAs and 16 upregulated lncRNAs. In 5-FU-resistant CRC cells, down-regulation of lncRNA snaR expression increases 5-FU sensitivity, overexpression of lncRNA CCAT1 (Colon cancer-associated transcript 1) reduced 5-FU sensitivity and apoptosis.[33] LncRNA H19 stimulates CRC tumor growth and chemoresistance through activating β-catenin pathway, and regulates SIRT1 to activate autophagy to promote 5-Fu resistance.[34] Besides, H19 overexpression results in resistance to 1,25(OH)2D3 through targeting miR-675-5p in colon cancer cells.[35] Methotrexate (MTX) resistance can be reduced by H19 knock out in MTX-resistant CRC cells.[36] Eisa et al have found that HOTAIR knockout regulates the expression of miR-203a-3p and activates the Wnt/β-catenin signaling pathway, which increases the sensitivity of CRC cells to DDP and PTX.[37] After treatment of HT-29 and HCT-116 cells with 5-FU, OXA, and IRT in vitro, the expression of LINC00973, LINC00941, lncRNA CASC19 (cancer susceptibility 19), CCAT1 (Colon cancer-associated transcript 1), and BCAR4 (Breast Cancer Anti-Estrogen Resistance 4) was significantly changed. LINC00973 is significantly increased, regulates the expression of DUSP/CDKN1A, promotes the proliferation of colon cancer cells, and inhibits apoptosis.[38] Other lncRNAs functions have not been determined and are worthy of further investigation.

Breast Cancer

The most common malignant tumor in women is breast cancer (BC). Trastuzumab, PTX, rapamycin (TOR), doxorubicin (DOX) and tamoxifen (TAX) play extremely important roles in breast cancer chemotherapy, but the efficacy of treatment

is hindered by drug resistance.[39] Approximately 70% of breast cancers are positive for estrogen receptor (ER), and TAX plays a crucial part in the treatment of estrogen receptor-positive primary BC, inhibiting tumor cell growth by binding to ERs and obstructing the signaling of ERs.[40]

There is considerable evidence that lncRNAs play roles in secondary resistance to TAX. LncRNA ROR (regulator of reprogramming) is an important biomarker of breast cancer, down-regulation of ROR could inhibit the expression of ZEB1 and ZEB2 by up-regulating the expression of miR-205, inhibit the EMT of breast cancer cells, and enhance the sensitivity of breast cancer cells to tamoxifen.[41] Furthermore, ROR promotes the survival of breast cancer cells during TOR treatment by functioning as a ceRNA sponge for miR-194-3p, which targets MECP2. ROR could downregulate mTOR levels to decrease angiogenesis, and then decrease the sensitivity of breast cancer cells to TOR. However, the lncRNA HOTAIR promotes the expression of estradiol-inducible genes and the transcription of the ER gene, thus inducing TAX resistance by increasing the level of ER protein and enhancing chromatin binding.[42] Sun et al reported that high H19 expression promotes autophagy in MCF-7/TAMR cells and reduces the response to TAX treatment. Otherwise, LOL (luminal lncRNA of luminal) is transcribed from a genomic locus of an enhancer to maintain its high expression in luminal BC and that it is extremely sensitive to enhancer-regulating factors, such as ZMYND8 and BRD4. Estrogen deprivation or ERα signaling pathway blockage can further stimulate LOL expression, which can promote tumor progression.[43] Trastuzumab is a human epidermal growth factor receptor 2 (HER2) inhibitor. Mesenchymal stem cells (MSC) culture-induced LncRNA AGAP2-AS1 (AGAP2 Antisense RNA 1) caused stemness and trastuzumab resistance via promoting CPT1 expression and inducing mitochondrial fatty acid β-oxidation (FAO).[44] Clinically, increased expression of serum exosome AGAP2-AS1 was associated with poor response to trastuzumab treatment. In conclusion, AGAP2-AS1 increased trastuzumab resistance via promoting ATG10 expression and inducing autophagy.[45]

Lung Cancer

Lung cancer is divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), DDP and gefitinib are important chemotherapy drugs.[46]

The resistance to CDDP is frequently associated with lncRNA. For example, low expression of lncRNA MEG3 (Maternally expressed gene 3) in CDDP resistant lung cancer cell-line A549/CDDP. Overexpression of MEG3 accelerated apoptosis; inhibited cell proliferation, migration and invasion; and induced G2/M + S phase cell cycle arrest in NSCLC, which can activate the production of proliferating cell nuclear antigen, cyclin A and cyclin E.[47] DDP resistance is significantly associated with OR3A4-CDK1 interaction. GAS5 expression was significantly reduced in NSCLC tissue samples, and upregulation of GAS5 inhibited the growth of NSCLC/CDDP cells and significantly reduced their migration and invasion.[48]

Gefitinib is a tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR), which has been used as the treatment of choice for locally advanced or metastatic NSCLC.[49] As mettl3-primed n6-methyladenosine (m6A) mRNA methylation occurs in NSCLC, YTHDF1/3 and eIF3b are recruited into the translation initiation complex to promote translation of YAP mRNA and enhance YAP mRNA stability by regulating the MALAT1-miR-1914-3p-YAP axis. Increased YAP expression results in drug resistance and metastasis.[50] LncRNA FENDRR (The FOXF1 Adjacent Noncoding Developmental Regulatory RNA) shows low expression in NSCLC and inhibits tumor growth. FENDRR enhancement inhibited chemotherapy resistance of A549/DDP cells to DDP. In A549/DDP cells, FENDRR inhibits chemotherapy resistance by modulating ABCC1, a member of the ABC transporter superfamily.[51]

Liver Cancer

Surgery is the traditional treatment for primary hepatocellular carcinoma (HCC). Sorafenib is the standard of care for unresectable or advanced liver cancer, but some patients are highly susceptible to drug resistance after treatment with sorafenib.[52] LncRNA TUC338 (transcribed ultraconserved element 338) is highly expressed in HCC tissues and cells. The expression of TUC338 was reduced in sorafenib-resistant HCC, its sensitivity to sorafenib was enhanced by up-regulating RASAL1. In vivo experiments also demonstrated that tumors transfected with siTUC338 were significantly reduced after sorafenib treatment.[53] Cheng et al found that LncRNA THOR may promote the growth and metastasis of HCC cells by enhancing the PTEN/AKT signaling pathway, and THOR knockdown could reduce the self-renewal ability of liver CSCs, inhibit the expansion of liver CSCs, and increase the sensitivity of liver cancer cells to sorafenib

chemotherapy.[54] Shi et al first discovered that LncRNA HANR was able to promote HCC progression through ceRNA mechanism, the expression of HANR was significantly increased in sorafenib-resistant cells, in which the autophagy-related proteins was significantly elevated, and apoptosis was reduced, suggesting that HANR enhances the sorafenib resistance by inducing autophagy.[55] Niu et al discover that LncRNA NEAT1 (nuclear enriched abundant transcript 1) expression was significantly increased in sorafenib resistant cells.[56] Tsuchiya et al found that NEAT1 in HCC was closely related to tumor stage, lymphatic metastasis and sorafenib resistance. Compared with the high NEAT1 expression group, patients in the low NEAT1 expression group showed a longer overall survival.[57] Moreover, Wu et al found that LncRNA HNF4A-AS1 (hepatocyte nuclear factor 4 alpha antisense RNA 1) and AL109659.2 were highly expressed, and both significantly enhanced resistance to sorafenib.[58]

Additionally, lncRNAs have been linked to drug resistance mechanisms in HCC chemotherapies. BE-7402/5-FU cells expressed twofold more lncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) than sensitive cells, and MALAT1 mediated resistance to 5-FU through interaction with miR-216b.[59] Otherwise, lncRNA HULC upregulate the expression of USP22 protein by adsorbing miR-6825-5p, miR-6845-5p, and miR-6886-3p. USP22 can reduce the ubiquitination degradation process of Sirt1, and maintaining its stability increases autophagy of HCC cells, which enhances the resistance of HCC to OXA.[60] It may provide new ideas for exploring how to reverse chemotherapeutic resistance in HCC.

Leukemia

Acute myeloid leukemia (AML) is the most commonly used chemotherapy drugs daunorubicin, cytarabine.[61] AML patients with high levels of lncRNA TUG1 (taurine-upregulated gene 1) have a poorer prognosis, and ADR-resistant.[62] In another clinical study, Hu et al reported that the expression of miR-96 was reduced in AML cell lines, while the expression of MALAT1 was increased, and that inhibition of MALAT1 improved the efficacy of cytarabine (Ara-C) in AML cells. In addition, in studies related to drug resistance in chronic leukemia, the expression of MALAT1 was increased in chronic myelogenous leukemia (CML) cells, and when MALAT1 was silenced, the proliferation and cell cycle arrest of CML cells were inhibited by target miR-328, the drug sensitivity of imatinib-resistant K562 cells was increased, and apoptosis was promoted.[63] Another study found that MEG3 promotes imatinib resistance in CML by regulating cell proliferation, apoptosis and expression of multi-drug resistance transporters in a sponge effect by binding to miR-21.[64] LncRNA UCA1, as an important regulator of MDR1, regulates imatinib resistance in CML cells by competitively binding miR-1 with MDR1.[65] Such resistance mechanisms are one of the main causes of drug resistance in Leukemia patients.

Pancreas

Pancreatic cancer poses significant challenges in its diagnosis and treatment due to its insidious onset, lack of specific clinical signs and symptoms, and absence of early diagnostic tests. Consequently, gemcitabine, the main therapeutic agent for pancreatic cancer, often encounters high rates of resistance, leading to treatment failure.[66] It has been observed that lncRNA HOTTIP (HOXA transcript at the distal tip), a highly expressed gene in pancreatic ductal adenocarcinoma tissues and cells, plays a crucial role. Downregulation of HOTTIP expression in pancreatic cancer cells slowed cell proliferation, arrested cells in G1 phase, reduced the EMT, and decreased the IC_{50} of tumor cells, suggesting that it could improve sensitivity to gemcitabine.[67] The mechanism may be mediated by the regulation of HOXA13 (homeobox protein Hox-A13) expression. In summary, lncRNAs have demonstrated their clinical applications in pancreatic cancer (Table 2).

Roles of LncRNA in Tumor Immune Escape

There is accumulating evidence that the expression of lncRNA regulates the activities of immune cells, neutrophils, monocytes, macrophages, dendritic cells (DC), T cells, and B cells, which are all implicated in tumor cell immune escape. Tumor immune evasion is a term used to describe the ability of tumor cells to evade detection and destruction by the immune system through alterations in their own characteristics or the surrounding microenvironment. The efficacy of immunotherapy is currently constrained by the phenomenon of tumor immune evasion.[68]

In this section, we will discuss the mechanisms by which lncRNA induces tumor immune escape from immune-related cells in a variety of tumors (Table 3).

Table 2 Differently Expressed LncRNA Associated with Tumor Drug Resistance

Tumor	LncRNA	Drug	Promote/Inhibit Resistance	Mechanism of Action	Ref
GC	AK022798	DDP	Promote	caspase-8, caspase-3	[24]
	UCA1	DDP, ADR,5-FU		miR-27b, caspase-3	[25]
	SNHG5	DDP		BAX and BCL-2 apoptosis	[26]
	PVT1	5-FU		BCL-2 apoptosis	[27]
	HOTAIR	DDP		PI3K/AKT Wnt/β-catenin signalings	[28]
	LINC01433	DOX DDP		YAP phosphorylation	[29]
	MALAT1	5-FU, CDDP, and vincristine		Increases ATG12	[30]
CRC	CCAT1	5-FU	Promote	P53/cMYC	[33]
	snaR	5-FU		Apoptosis	[33]
	H19	5-FU /1,25(OH)2D3/ MTX/oxa		miR-675-5p, β-catenin signalings	[34]
	HOTAIR	Cisplatin/paclitaxel/ Diacerein		miR-203a-3p, Wnt/ β-catenin signaling	[37]
	LINC00973	Oxaliplatin/5-FU/Irinotecan		DUSP/CDKN1A	[38]
	LINC00941	Oxaliplatin/5-FU/Irinotecan	–	–	[38]
	CASC19	Oxaliplatin/5-FU/Irinotecan	–	–	[38]
	BCAR4	Oxaliplatin/5-FU/Irinotecan	–	–	[38]
BC	ROR	Tamoxifen/ Rapamycin	Promote	miR-205, ZEB1, ZEB2/ MECP2	[41]
	HOTAIR	Tamoxifen		ER, transcription	[42]
	H19	Tamoxifen		SAHH/DNMT3B	[44]
	LOL	Tamoxifen		Estrogen deprivation or blockage of the estrogen receptor alpha/ transcription	[43]
	AGAP2-AS1	Trastuzumab		CPT1/ ATG10, mitochondrial fatty acid β-oxidation	[44,45]
NSCLC	MEG3	CDDP	Inhibit	G2/M + S phase	[47]
	OR3A4	DDP	Promote	MALAT1-miR-1914-3p-YAP	[48]
	GAS5	CDDP		miR-222	[48]
	YTHDF1/3	DDP		MALAT1-miR-1914-3p-YAP	[50]
	FENDRR	DDP		ABCC1 drug efflux system	[51]
HCC	TUC338	Sorafenib	Promote	RASAL1	[53]
	THOR	Sorafenib		PTEN/AKT signaling pathway	[54]
	HANR	Sorafenib		miR-29b/ATG9A	[55]
	NEAT1	Sorafenib		miR-149-5p/AKT1	[56,57]
	HNF4A-AS1	Sorafenib		-	[58]
	AL109659.2	Sorafenib		-	[58]
AML	TUG1	Cytarabine	Promote	miR-96 /Ara-C	[62]
	MALAT1	Cytarabine		miR-328, cell cycle	[63]

(*Continued*)

Table 2 (Continued).

Tumor	LncRNA	Drug	Promote/Inhibit Resistance	Mechanism of Action	Ref
CML	MEG3	Imatinib	Promote	miR-21	[64]
	UCA1	Imatinib		miR-1, MDR1	[65]
PAAD	HOTTIP	Gemcitabine	Promote	Proliferation / G1 phase /cell cycle/EMT	[67]

Table 3 LncRNA Involved in Tumor Immune Escape

Immune Cell	LncRNA	Promote/Inhibit Escape	Mechanism of Action	Ref
TAM	Dnmt3aos	Promote	DNA methylation	[69]
	AFAP1-AS1		miR-26a /translation	[70]
	PCAT6		miR-326 and RhoA/ROCK	[71]
TAM/T-cell	HOTTIP	Promote	STAT3/PD-L1 signaling	[72]
DCs	LINC00963	Promote	miR-612, translation	[73]
NK	GAS5	Inhibit	miR-544/RUNX3	[74]
TH2	MAF4	Promote	IFNγ cytokine	[75]
TH1	NeST		WDR5, IFN-γ	[76]
Treg	SNHG1	Promote	miR-448/IDO	[77]
T cell	CECR7	Promote	miR-429/CTLA4	[78]
TH1/CTL	NEAT1	Inhibit	cGAS-STING-IRF3	[79,80]
CTL	NKILA	Inhibit	NF-κB signalings	[74]
	LINC00473	Promote	miR-195-5p, PD-L1	[81]
	KCNQ1OT1		MiR-30a-5p/USP22, PD-L1 Ubiquitination	[81]
	SNHG14		miR-152-3p	[81]

Effects of LncRNAs on Innate Immune Cells

Clinical studies have shown that prognosis is related to the proportion of macrophages in tumor tissue. Tumor-associated macrophages (TAM) can suppress the immune system in a variety of ways.[82] In M2 macrophages, the lncRNA Dnmt3aos (DNA methyltransferase 3A, opposite strand) is highly expressed and regulates the expression of Dnmt3a, which regulates the expression of interferon-gamma (IFN-γ), a protein related to polarization, in macrophages by modifying DNA methylation. TAM polarization is directly related to tumor immune escape.[69] Exosomes produced by cancer cells can encourage immune responses that support the tumor. Subsequent investigations showed that M2 macrophage-derived exosomes could transport extracellular AFAP1-AS1 into KYSE410 cells. TAM-released exosomes in esophageal cancer decrease the levels of miR-26a and increase the expression of AFAP1-AS1, consequently promoting migration, invasion, and the spread of cancer to the lungs.[70] The results also suggest that exosomes carry lncRNA, all involved in immune cell-to-cell communication.

However, some lncRNAs are aberrantly regulated in tumor cells and immune cells, but their origins are unknown. For example, M2 macrophages in cholangiocarcinoma, lncRNA PCAT6 (Prostate cancer-associated transcript 6) is increased, which leads to the generation of reactive oxygen species via miR-326 and RhoA/ROCK signaling, and results in the disruption of macrophage mitochondrial and metabolic functions. The M2-like Macrophage Polarization ultimately leads

to the immune escape of tumors.[71] The correlation between TAM and lncRNAs in TME is limited, but most of lncRNAs influence the anti-tumor effect by regulating the expression of cytokines. For example, in ovarian cancer, lncRNA HOTTIP regulates the transcription factor c-Jun(c-Jun) to promote IL-6 expression, which activates the STAT3/PD-L1 pathway in TAM and inhibits T-cell proliferation.[72]

It has been demonstrated that lncRNAs play an important role in the differentiation and maturation of DCs in the TME and in the migration of tumor cells. For instance, the expression level of LINC00963 in GC is significantly correlated with patient lymph node metastasis, which can inhibit the differentiation and maturation of DCs by competitively binding to miR-612.[73] Otherwise, Inc RNAs enhance the killing function of NK cells. In HCC, GAS5 is significantly down-regulated in NK cells, and overexpression of GAS5 enhances the expression of IFN-γ and the killing ability of NK cells by affecting the miR-544/RUNX3 axis.[74]

Effect of LncRNAs on Adaptive Immune Cells

Since there are few studies on the correlation between B lymphocytes and lncRNAs in the TME, in this chapter, we will discuss how Treg cells and CTLs interact with lncRNAs in the TME and influence immune cell proliferation and differentiation, and even the process of tumor development and metastasis.[83]

Immunosuppressive T-cell (Treg, Th2) enrichment and anti-tumor T-cell (CTL, TH1) deficiency promote tumor immune escape. A low expression of NEAT1 enhances $CD8^+$ T cell antitumor function in patients with HCC.[79] Jafari et al showed that lncRNA MAF4 (MADS AFFECTING FLOWERING 4) was negatively correlated with MAF, a TH2-associated transcription factor, and that inhibited TH1 to TH2 differentiation, affecting the anti-tumor immune response of T cells.[75] LncRNA NeST also regulates the differentiation of TH1 cells, and interacts with histone methyltransferase WD repeat-containing protein 5 (WDR5) to regulate the transcription of adjacent IFN γ genes in Th1 cells to modulate anti-tumor immune response.[76] LncRNA SNHG1 (small nucleolar RNA host gene 1) regulates Treg cell differentiation through the miR-448/IDO pathway influencing the immune escape of BC cells.[77] Yao et al showed that lncRNA CECR7 regulate the expression of cytotoxic T lymphocyte associated protein 4 (CTLA4) by targeting miR-429, downregulation of CECR7 can increase the surface of CTLA4 on the cell surface. Therefore, lncRNA may be a target for enhancing the therapeutic effect of CTLA-4.[78] Cytotoxic T lymphocytes (CTLs) can be dysfunctional or even depleted during tumor immune escape. LncRNAs also affect CTLs proliferation by participating in other signal pathways. For example, knockdown of lncRNA NEAT1 in lung cancer cells activated the cGAS/STING signal pathway and promoted the expression of CXCL10, CCL5 and IFNβ, and the proliferation of CTLs;[80] In BC, NKILA (NF-kappaB-interacting lncRNA) increases the sensitivity of CTLs to activation-induced cell death (AICD) and reduces the proportion of CTLs by inhibiting NF-κB.[84]

Otherwise, lncRNAs can competitively bind miRNAs to indirectly affect the expression of PD-L1, inhibiting the proliferation of CTLs in the TME. For instance, knockdown LINC00473 in pancreatic cancer cells resulted in down-regulation of IL-10 and PD-L1 expression, while the expressions of IL-4 and IFN-γ and the apoptosis of CTLs cells and the proportion is increased. Similar to the above studies, KCNQ1OT1 (potassium voltage-gated channel subfamily Q member 1 opposite strand 1) and SNHG14 (small nucleolar RNA host gene 14) can also indirectly inhibit the proliferation of CTLs in the TME.[81]

Clinical Implications of LncRNAs in Chemotherapy Resistance
Biomarkers

Early detection, accurate diagnosis, and effective treatment are key to improving cancer patient survival rates.[85] LncRNA shows promise as a highly specific and sensitive tumor marker that can be easily measured and repeated in various fluid specimens.[86] The identification of lncRNA PCA3 in urine of prostate cancer patients was a major breakthrough in diagnosing prostate cancer.[87] LncRNA HULC was found to be highly expressed in liver cancer tissues and blood samples.[88] LncRNA H19 levels were significantly higher in plasma of gastric cancer patients compared to healthy individuals, decreasing after surgery.[89] Furthermore, Tang et al found tumor-related lncRNAs in oral cancer patients' saliva, indicating their potential for early diagnosis and postoperative monitoring.[90]

Despite years of progress, challenges remain in using lncRNA as cancer biomarkers. The lack of tissue-specific lncRNAs and uncertainty about their presence in plasma due to tumorigenesis are significant obstacles.

Therapeutic Potential

The significant role of lncRNAs in the emergence of cancer drug resistance has been demonstrated in numerous studies. These molecules can act as either oncogenic drivers or tumor suppressors, exhibiting dual functionalities in the context of cancer development based on their specific downstream targets.[91] The unique attributes of lncRNAs position them as promising candidates for therapeutic intervention in cancer treatment. Furthermore, due to their crucial roles in cancer progression and resistance to treatment, lncRNAs are regarded as potential targets for therapeutic strategies in cancer patients.[92] Direct delivery of tumor-suppressive lncRNAs and silencing oncogenic lncRNAs show promise for enhancing cancer treatments, but face challenges like drug toxicity and off-target effects.[93] Therefore, it is crucial to improve the safety and effectiveness of lncRNA-based cancer therapy through the development of better delivery methods. More clinical trials are needed to advance these therapeutic strategies and help cancer patients.[94]

Application in Immunotherapy

Recent studies have shown that lncRNAs can be used as targets for CAR-T therapy. Silencing of lncRNA INCR1 (IFN-stimulated non-coding RNA 1) decreased the expression of PD-L1, JAK2 and several other IFN-γ-stimulated genes. Knockdown of INCR1 sensitizes tumor cells to cytotoxic T-cell-mediated killing, thereby improving CAR-T efficacy.[95] Clinically, overexpression of lncRNA NKILA in tumor-specific CTL and TH1 cells is associated with their apoptosis and shorter patient survival.[84] LncRNA RN7SL1 is expressed in exosomes secreted by CAR-T, which enables CAR-T to be amplified and not easily depleted. Moreover, RN7SL1 activates RIG-1 receptor, which activates dendritic cells and myeloid cells, enhances the immune response and inhibits the transformation of myeloid cells into myeloid-derived suppressor cells (MDSC).[96] Previously, we have discussed the regulatory relationship between lncRNAs and PD-L1/PD-1, which may also enhance future PD-L1/PD-1 inhibitor sensitization.

Conclusion

In biological tumor progression, lncRNAs are recognized as important regulators. As they have multiple functions in cancer cells, including epigenetic regulation, lncRNAs play a central role in regulating both intracellular activities and the extracellular microenvironment. In recent studies, lncRNAs have been found to impact the sensitivity of tumor cells to chemotherapy by participating in many cellular and genomic process. It is becoming increasingly obvious that long noncoding RNAs play a role in regulating immune cells, as well as escaping tumor immune responses. In the treatment of malignant tumors, lncRNA are important as diagnostic biomarkers and therapeutic targets because they regulate immune checkpoints.[97] Current immunotherapeutic strategies focus mainly on T cell-mediated immunotherapy, further research is required regarding how the interactions between lncRNA and other immune cells, antigen presenting cells, and chemokines mediate immune escape.[98]

In part due to the complex immune system, researchers are only just beginning to understand how lncRNAs play a role in tumorigenesis. With regard to tumor resistance to immune checkpoint inhibitors and other chemotherapeutic agents, we emphasize the potential of lncRNAs for use in cancer therapy. Future study of lncRNAs may result in the development of methods to reverse resistance to chemotherapeutic drugs by regulating gene expression and allow the development of tumors to be affected by artificially upregulating or downregulating specific target genes. LncRNA can increase the sensitivity of tumors to chemotherapy drugs, thereby improving the efficacy of chemotherapy, and is a potential target to overcome tumor drug resistance. An improved understanding of lncRNAs will provide insight into their precise roles and may facilitate their use to both monitor disease progression and to develop novel therapeutic interventions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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