


The Crosstalk Between Long Non-Coding RNAs and Various Types of Death in Cancer Cells

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Abstract

With the increasing aging population, cancer has become one of the leading causes of death worldwide, and the number of cancer cases and deaths is only anticipated to grow further. Long non-coding RNAs (lncRNAs), which are closely associated with the expression level of downstream genes and various types of bioactivity, are regarded as one of the key regulators of cancer cell proliferation and death. Cell death, including apoptosis, necrosis, autophagy, pyroptosis, and ferroptosis, plays a vital role in the progression of cancer. A better understanding of the regulatory relationships between lncRNAs and these various types of cancer cell death is therefore urgently required. The occurrence and development of tumors can be controlled by increasing or decreasing the expression of lncRNAs, a method which confers broad prospects for cancer treatment. Therefore, it is urgent for us to understand the influence of lncRNAs on the development of different modes of tumor death, and to evaluate whether lncRNAs have the potential to be used as biological targets for inducing cell death and predicting prognosis and recurrence of chemotherapy. The purpose of this review is to provide an overview of the various forms of cancer cell death, including apoptosis, necrosis, autophagy, pyroptosis, and ferroptosis, and to describe the mechanisms of different types of cancer cell death that are regulated by lncRNAs in order to explore potential targets for cancer therapy.

Keywords

lncRNAs, apoptosis, necrosis, autophagy, pyroptosis, ferroptosis, cancer

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Introduction

With the increasing aging population, cancer has become one of the leading causes of death worldwide, and the number of cancer cases and deaths is only anticipated to grow further. Cancer is characterized by disturbed signals¹ and an unnatural disordered pattern formed by a large number of genetic and epigenetic changes that are related to the ultra-conservative, non-coding elements of the genome sequence.² Aging and a poor lifestyle increase the risk of cancer,³ however, with the improvement of living standards, many lifestyle risk factors, such as smoking, lack of exercise, obesity, and reproductive patterns, have been widely reduced in high-income countries.⁴ Despite this, due to the aging global population, researchers predict that in 2040 the number of cancer patients will exceed 29.5 million worldwide.⁵

Cancer tissues are composed of high quantities of aggregated cancer cells and a small quantity of cancer stem cells.⁶ The progression of cancer is a complex and multi-step process.⁷ Although cancer occurs in a mutated cell, it can develop

into extremely heterogeneous, abnormally differentiated, proliferating cells with different markers.⁸ This heterogeneity can explain the variety in cancer prognosis, recurrence, metastasis, and drug resistance.^{7,9} Changes in transcription patterns are frequently observed in many illness, including human cancers.¹⁰ Changes in the transcriptome are not only related to the RNAs that code for proteins but also involve the abnormal expression of multiple non-coding elements of the human genome.¹¹

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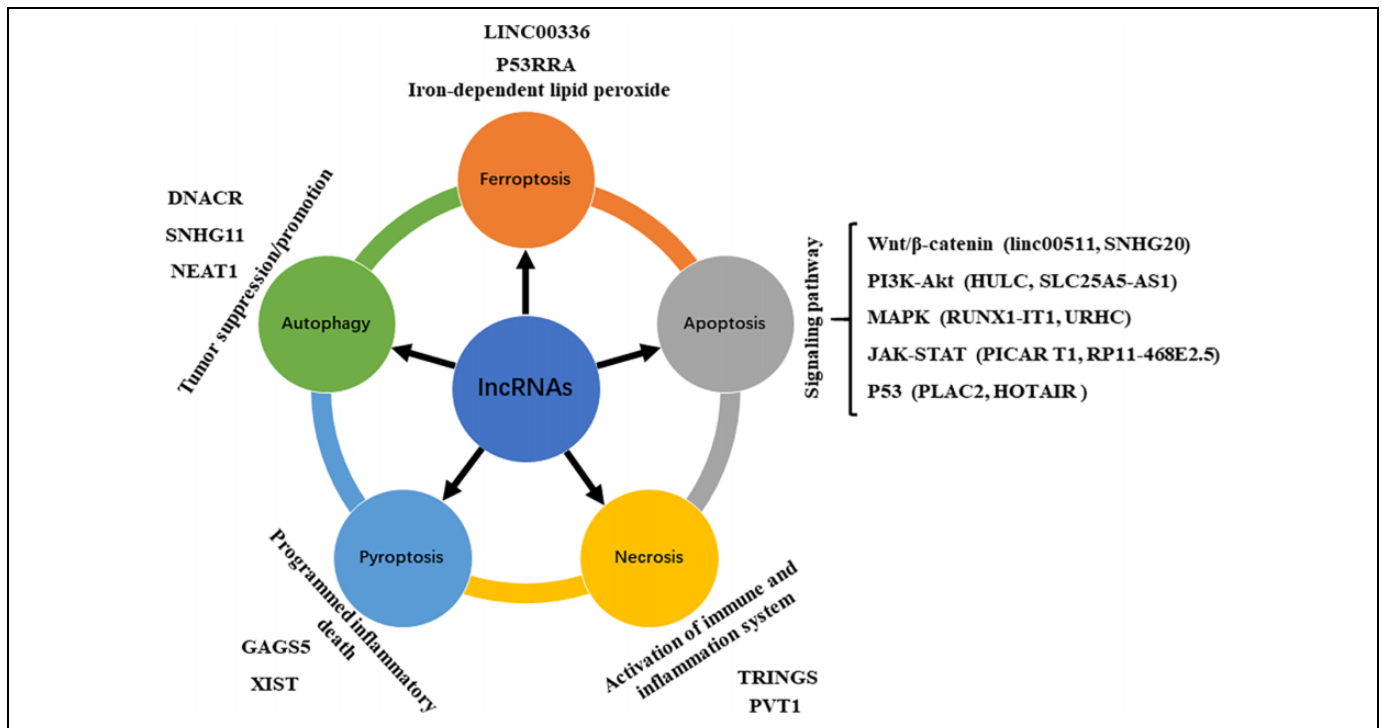


Figure 1. Overview of crosstalk between long non-coding RNAs and various types of death in cancer cells.

Long non-coding RNAs (lncRNAs) are transcripts that are longer than 200 nucleotides.¹² The competition between lncRNAs and protein-coding mRNAs to bind to miRNAs is the most widely accepted competitive endogenous RNA (ceRNA).¹³ LncRNAs play key roles in gene regulation, and therefore affect all aspects of homeostasis, including proliferation, survival, migration, and genome stability.¹⁴ LncRNA can increase or decrease the expression of mRNA.¹⁵ With the rapid development of sequencing technology, it is becoming increasingly clear that regions that do not code for proteins play an important role in the occurrence and development of cancer.¹⁶ Many lncRNAs are located in somatic copy number changes (SCNAs),¹⁷ amplified or deleted regions of the genome which arise due to the inherent genomic instability of cancer cells.¹⁸ Epigenetic changes in DNA methylation are important regulators of lncRNA expression, which can interfere with the expression pattern of lncRNAs and promote tumorigenesis.¹⁹ LncRNAs regulate a variety of biological activities that have an important impact on humans through its expression in different types of cancer.²⁰ In the past 2 decades, the roles of non-coding RNAs (ncRNAs) have been widely studied in both healthy body conditions and in disease.²¹ Through the coding of lncRNA in cancer, we divide these lncRNAs into 2 categories: lncRNAs related to tumor suppression (e.g., LED, Linc-p21, GUARDIN, PTENP1) and lncRNAs related to tumor promotion (e.g., MALAT1, HOTAIR, NORAD, PVT1).² The regulatory loop between microRNAs and lncRNAs has an active function in translational regulation and transcription and is related to cancer.²⁰ LncRNA can affect miRNA expression and thus exert its function. Many studies have found that the

pathogenesis of some diseases is influenced by the changes of lncRNA in autophagy, apoptosis, pyroptosis, ferroptosis, thus causing disease. Therefore, as a new biological marker, lncRNA has great potential in cancer diagnosis and its role as an important gene expression regulator²² can be used as a therapeutic target.

The abnormal utterance of lncRNAs has been widely reported in various cancers. A large numbers of regulatory genes are involved in the mechanisms by which animals adjust mitosis, discover cell abnormalities, and initiate programmed cell death.²³ Mitosis is stimulated by some of these regulatory genes, while other regulatory genes inhibit mitosis or cause programmed cell death. For cancer and other diseases characterized by the regulation of abnormal cell death, studying the mechanisms of different types of cell death is important.²⁴ LncRNAs not only influence the development of different tumor death modes, but also have the potential to induce cell death, predict the prognosis and recurrence of chemotherapy.²⁵ In the present study, we provide an overview of the various forms of cancer cell death, including apoptosis, necrosis, autophagy, pyroptosis, and ferroptosis, and describe the regulatory roles of lncRNAs in these mechanisms (Figure 1).

The Regulatory Effect of Long Non-Coding (lncRNAs) on Tumor Cell Apoptosis

Apoptosis is a form of programmed cell death (PCD) that was first discovered in animals in 1972.²⁶ The morphological and biochemical characteristics of apoptosis make it easily distinguishable from other forms of cell death. At the beginning of

apoptosis, morphological changes in membrane permeability occur, which depend on the biochemical mechanism of energy. Single-celled apoptotic mechanisms have roles that include family-selected altruistic suicide, population size control, sharing common objects, and responding to viral infections. Interestingly, apoptotic factors also contain non-apoptotic functions.²⁷ Apoptosis is associated with cell senescence in eukaryotes and is an important component of the inhibition mechanism of congenital tumors.^{28,29} Apoptosis exists not only as a homeostatic mechanism for maintaining the number of cells in a tissue during development and aging, but also as a defense mechanism; for example, in immune responses or when cells are damaged by disease.³⁰ Although various stimulations and conditions can trigger apoptosis, not all cells that die are exposed to the same stimulants. For example, radiotherapy or chemotherapy, used in cancer therapy, can cause DNA damage in certain cells, leading apoptosis through various pathways. Overexpression or low expression of apoptosis can be attributed to a large number of human diseases. The regulation of cell death and survival is therefore a promising target for treatment.³¹ The key to apoptosis is to determine whether pro-apoptotic and anti-apoptotic protein regulators are balanced. Potentially harmful cells can be eliminated by apoptosis that is caused by DNA damage in precancerous lesions, thus blocking tumor growth.³² In recent years, it has been reported that the occurrence and development of tumors and the tolerance to treatment are affected by apoptosis. In clinical treatment, anticancer drugs that stimulate the intact apoptotic signaling pathways are used to accelerate cancer cell death.³³

However, drug resistance can limit the effectiveness of treatment that regulates the abnormal activation/suppression of signaling pathways.³⁴ Therefore, increasing the efficacy of drugs and preventing drug resistance is the focus of apoptosis research.²⁷ Apoptosis can be initiated by lncRNAs either by regulating apoptosis-related receptors or as cerRNAs. Many signaling pathways, such as the Wnt/ β -catenin, PI3K/Akt, and Mitogen-activated protein kinase (MAPK) signaling pathways have been found to participate in cancer cell apoptosis (Table 1).

Wnt/ β -Catenin Signaling Pathway

The Wnt/ β -catenin signaling pathway is considered one of the most important signaling pathways of evolution and physiological/pathophysiological processes. The Wnt/ β -catenin signaling pathway is activated once it combines with the relevant ligands.⁴⁹ The signal transduction mechanism of the Wnt/ β -catenin pathway is highly complex and conservative. Physiological and pathological processes in the human body, including hepatobiliary development and maturation, are regulated by this pathway.⁵⁰ In a healthy mature liver, the Wnt/ β -catenin pathway is mostly inactive; however, it can be reactivated in the occurrence and development of certain diseases and cancers.⁵¹ Wnt/ β -catenin signaling is often over-activated in 2 of the most common primary liver cancers in adults: hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), promoting tumor growth and spread. A significant proportion of liver tumors have mutations in genes that encode key components of the Wnt/ β -catenin signaling pathway.^{35,52} The

Table 1. The Regulatory Effect of lncRNAs on Tumor Cell Apoptosis.

lncRNAs	Expression	Signaling pathway	Function	Reference
LINC00511	Down	Wnt/ β signaling pathway	LncRNA LINC00511 suppresses proliferation and promotes apoptosis of bladder cancer cells	35
MALAT1	Up		LncRNA MALAT1 regulates ovarian cancer cell proliferation, migration and apoptosis	36
SNHG20	Up		LncRNA SNHG20 promotes the proliferation and inhibits the apoptosis of NSCLC cells by targeting miR-197	37
SLC25A5-AS1	Down	PI3K/AKT signaling pathway	SLC25A5-AS1 facilitates cell growth and inhibits apoptosis	38
HULC	Up		LncRNA HULC promotes non-small cell lung cancer cell proliferation and inhibits the apoptosis	39
LINC00982	Up		LINC00982 inhibits cell proliferation and promotes cell apoptosis	40
HCG11	Up	MAPK signaling pathway	Modulation of IGF2BP1 by lncRNA RNA HCG11 suppresses apoptosis of hepatocellular carcinoma cells	41
URHC	Up		LncRNA URHC Regulates Cell Proliferation and Apoptosis via ZAK	42
RUNX1-IT1	Down		LncRNA RUNX1-IT1 inhibits proliferation and promotes apoptosis of hepatocellular carcinoma	43
PICART1	Down	JAK-STAT signaling pathway	LncRNA PICART1 suppresses proliferation and promotes apoptosis in lung cancer cells	44
LncRNA-135528	Up		LncRNA-135528 inhibits tumor progression by up-regulating CXCL10	45
RP11-468E2.5	up		Long non-coding RNA RP11-468E2.5 curtails colorectal cancer cell proliferation and stimulates apoptosis	46
PLAC2	Down	P53	LncRNA PLAC2 upregulates p53 to induce hepatocellular carcinoma cell apoptosis	47
HOTAIR	Down		HOTAIR may regulate proliferation, apoptosis, migration and invasion of MCF-7 cells	48

Wnt/ β -catenin signaling pathway's main role is in the apoptosis of cancer cells. Wnt is overexpressed in many human cancers, and the prognosis of cancer is closely related to this phenomenon.⁵³ LncRNA is widely involved in the apoptosis of various tumor cells via regulation of the Wnt/ β -catenin pathway.

Long non-coding RNA linc00511 has been demonstrated to be overexpressed in bladder cancer tissues and cells. Linc00511 not only causes cell proliferation inhibition and limits the cell cycle but also helps to increase apoptosis, processes that may be interrelated via inhibition of the activation of the Wnt/ β signaling pathway. They discovered that the functions of linc00511, which was found to promote apoptosis and reduce cell proliferation in bladder cancer, played a role via the Wnt/ β signaling pathway, thereby forming a potential target for bladder cancer treatment.³⁵ The relative expression of MALAT1 has been found to be abnormally upregulated in ovarian cancer tissues and cell lines. The upregulation of MALAT1, which is associated with poor prognoses in ovarian cancer patients, promotes the proliferation, invasion, and migration of ovarian cancer cells, accelerated the S phase of the cell cycle, and inhibited cell apoptosis. The upregulation of MALAT1 has also been found to increase the expression levels of DVL2, β -catenin, and cyclin D1 in SKOV3 and HO8910 cells and to decrease the expression levels of GSK-3. Additionally, the inhibition of cell invasion and migration reversed MALAT1 downregulation via SKL2001-activation of the Wnt/ β -catenin signaling pathway.³⁶ LncRNA SNHG20 was found to be highly expressed in the serum and cancer tissues of non-small-cell lung cancer (NSCLC) patients. The low expression of lncRNA SNHG20 can inhibit NSCLC cell proliferation and accelerate cell apoptosis. LncRNA SNHG20 can bind to micro RNA (miR)-197, and nuclear transposition of β -catenin was found to be significantly enhanced after miR-197 transfection. After small interfering RNA (siRNA) downregulated miR-197, the key molecules of the Wnt/ β -catenin pathway (TCF and LEF1) were significantly downregulated.³⁷

PI3K-Akt Signaling Pathway

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway is considered the key pathway in carcinogenesis.⁵⁴ The action of PI3K leads to the phosphorylation (and thus activation) of Akt to p-Akt, and this effect is antagonized by PTEN. The central role of PI3K/Akt signaling in complex cellular processes makes this pathway very important in cancer cells, and the over-expression of p-Akt seems to be associated with poor overall survival rates in certain types of cancer.⁵⁵ Akt is very important because its downstream cytoplasmic and nuclear target proteins are phosphorylated and connect Akt to numerous connected signaling pathways.⁵⁶ Various physiological processes are regulated by Akt, including the cell cycle, DNA repair, protein synthesis, and carbohydrate metabolism.⁵⁷ Thus, the PI3K-Akt signaling pathway is essential not only for many aspects of physiology, but also for many pathological conditions. In different types of tumors, such as solid tumors and

blood tumors, mutations in key genes have been found to affect this signaling pathway.⁵⁸ Due to the activation of the PI3K/Akt pathway, the control of cell growth and survival is severely disturbed, resulting in competitive growth advantages, metastatic ability, angiogenesis, and treatment resistance.⁵³ Therefore, this composite pathway is considered to be one of the most attractive targets for the development of anticancer drugs.⁵⁹

The expression of SLC25A5-AS1 in normal tissues that lie adjacent to cancer tissues is lower than in gastric cancer (GC) tissues and is closely related to tumor size, TNM staging, and lymph node metastasis. In addition, SLC25A5-AS1 can inhibit GC cell proliferation *in vitro*, and induce G1/G1 cell cycle arrest and apoptosis, and GC growth *in vivo*. SLC25A5-AS1 has the potential to be used as a competitive endogenous RNA (ceRNA) to participate in the de-inhibition of miR-19a-3p target gene PTEN expression, and regulate the malignant phenotype via the PI3K/AKT signaling pathway.³⁸ The expression level of highly-upregulated in liver cancer (HULC) lncRNA in tumor tissues of most patients has been found to be significantly higher than that in normal tissues, and the serum HULC level of healthy controls is lower than that of cancer patients. As the primary tumor stage (T stage) increases, the serum HULC level increases. Serum HULC level is directly proportional to NSCLC and its prognosis. Tumor cell proliferation and apoptosis are also related to HULC. The expression level of SPHK1 and the phosphorylation level of Akt are correlated with the expression level of HULC, and also significantly affect the expression of Akt. The proliferation of NSCLC cells can be regulated by low-expressing lncRNA-HULC via the downregulation of sphingosine kinase 1 (SphK1).³⁹ LINC00982 expression in tumor tissues was found to be lower than in adjacent tissues and was related to the tumor size and TNM stage. Decreasing the expression of LINC00982 can promote the proliferation and apoptosis of ACHN and A-498 cells. Meanwhile, the activity of the PI3K/AKT signaling pathway can be regulated by the expression level of LINC00982. Therefore, reducing the expression of LINC00982 can promote the proliferation of renal cancer cells and reduce cell apoptosis via regulation of the activity of the PI3K/AKT signaling pathway.⁴⁰

Mitogen-Activated Protein Kinase (MAPK) Signaling Pathway

MAPK is a serine-threonine protein kinase that regulates various cellular activities, including proliferation, differentiation, apoptosis, survival, inflammation, and innate immunity.⁶⁰ MAPK is therefore an important component of the physiological and pathological processes involved in cell growth and survival. Abnormal MAPK signaling not only leads to the occurrence and development of human cancer cells, but can also help us to evaluate the efficacy of cancer treatment.⁶⁰ The MAPK signaling pathway also affects other diverse human diseases, including neurodegenerative disorders such as Alzheimer's disease.⁶¹ In mammalian cells, the most important

negative regulatory protein in the MAPK signaling pathway is MAPK phosphatase (MKP). MKP's participation in normal or abnormal human activities is closely related to the occurrence and development of cancer.⁶² The expression of MKP is closely related to drug resistance in cancer treatment, making MKP a potential target for cancer treatment.^{63,64}

The expression of HCG11 and insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) in paracancerous tissues is significantly lower than in liver cancer tissues. Upregulation of these 2 indexes results in increased HepG2 cell activity, proliferation, and migration; while cell apoptosis and G1 cell cycle arrest occur after HCG11 and IGF2BP1 gene silencing. In addition, the activities of HCG11 and IGF2BP1 are activated, which promotes the phosphorylation of anti-apoptotic factors such as ERK, JNK, and P38. Mitochondrial apoptosis is initiated by the activation of P21 and cleavage of caspase-3. HCG11, by interacting with IGF2BP1, activates MAPK signaling and ultimately promotes hepatocellular carcinoma (HCC) progression.⁴¹ URHC expression has been found to be increased in hepatoma cells and HCC tissues, and its high expression is associated with poor overall survival. High URHC expression can increase cell proliferation and reduce cell apoptosis. In HCC tissues, the mRNA level of leucine-zipper-containing kinase AZK (ZAK) is downregulated, and the expression level of ZAK is negatively correlated with the expression level of URHC; therefore, ZAK is thought to be involved in URHC-mediated cell proliferation and apoptosis. In addition, the inactivation of the MAPK pathway partly explains the cell growth and apoptosis induced by URHC-ZAK. Therefore, low expression of URHC can inhibit cell proliferation and increase apoptosis by increasing the expression of the MAPK pathway. These findings suggest new therapeutic methods and potential therapeutic targets for the treatment of liver cancer.⁴²

RUNX1-IT1 expression in HCC tissues is lower than in normal tissues. Silencing lncRNA-RUNX1-IT1 can significantly induce proliferation and reduce apoptosis of hepatocellular carcinoma cells. Conversely, the highly expressed lncRNA-RUNX1-IT1 gene can significantly inhibit the proliferation ability of HCC cells and promote apoptosis. Overexpressed lncRNA-RUNX1-IT1 suggests a better prognosis in patients with liver cancer. LncRNA-RUNX1-IT1 plays an important role in the development and progression of HCC by participating in cell proliferation and apoptosis, and its role is closely related to the MAPK signaling pathway. Therefore, lncRNA-RUNX1-IT1 may be a strong candidate for a prognostic biomarker and therapeutic target of HCC.⁴³

JAK-Signal Transducers and Activators of Transcription (STAT) Signaling Pathway

The key proteins of multi-membrane receptor-mediated signal transduction are the Janus tyrosine kinase (JAK) family. Important downstream factors, such as STATs, are related to JAK2, and downstream factors in turn regulate the expression of a variety of proteins involved in the induction and inhibition of

apoptosis.⁶⁵ The JAK-STAT signaling pathway promotes cell proliferation, survival, and differentiation. Important biological phenomena, such as hematopoietic function, immune function, breast development, and lactation, etc. all play a role by coordinating the organized basic cell functions mediated by the JAK/STAT signaling pathway.⁶⁶ Some human diseases are caused by germline mutations in JAK-STAT, especially mutations in the immune system. Uncontrolled cell proliferation promotes the growth of tumors and myeloproliferative diseases⁶⁷ due to functional transformation of somatic cells in JAK-STAT signal transduction. Therefore, the JAK/STAT signal axis is an important pathway for the proliferation and survival of different tumor cells, and may even play an important role in the mechanism of molecular-targeted drug resistance.^{68,69}

PICAR T1 expression in human lung cancer tissues and cell lines is lower than in normal tissues. Promoting the expression of PICAR T1 can reduce the survival rate of lung cancer cells. However, low expression of PICAR T1 promotes the cell cycle progression of SPC-A-1 and NCI-H1975 cell lines and inhibits cell apoptosis. Low PICAR T1 expression also accelerates migration, as evidenced by downregulation of E-cadherin and upregulation of Twist1, MMP2, and MMP9. In addition, in our previous study we found that promoting PICAR T1 expression may regulate apoptosis and migration by inhibiting the JAK2/STAT3 pathway. *In vivo* experiments have shown that the silencing of the *PICAR T1* gene significantly promotes tumor formation. This study showed that inhibiting the expression of PICAR T1 could promote the growth and metastasis of lung cancer cells. In addition, PICAR T1 may play a role in tumor inhibition by regulating the JAK2/STAT3 pathway.⁴⁴ Highly expressed lncRNA135528 promotes apoptosis of glioma cells, inhibits cell proliferation, and prevents cell cycle progression. Inhibiting the expression of lncRNA135528 can lead to a significant decrease in the level of CXCL10 in glioma cells and differential expression of mRNA related to the JAK/STAT pathway. Therefore, silencing lncRNA135528 can inhibit CXCL10 via the JAK/STAT pathway, thereby promoting tumor progression. This provides a new target for tumor treatment.⁴⁵

The expression of RP11-468E2.5 in normal tissues is larger than in colon cancer tissues, and the expressions of STAT5, STAT6, and cell cycle marker cyclin1 (CCND1) are lower. RP11-468E2.5 has been confirmed to participate in the JAK/STAT signaling pathway through STAT5 and STAT6. siRNA treatment for RP11-468E2.5 was found to increase the expression of STAT5, STAT6, and CCND1, while decreasing the expression of P21 and P27. However, after treatment with AG490, it inhibited the proliferation of CRC cells and promoted cell apoptosis and inhibited cell cycle entry. Conversely, siRNA treatment for RP11-468E2.5 gave the opposite result to AG490: AG490 treatment reversed these results. In summary, silencing RP11-468E2.5 can activate the JAK/STAT signaling pathway by targeting STAT5 and STAT6, thereby promoting the proliferation of colorectal cancer cells and inhibiting cell apoptosis.⁴⁶

P53 Signaling Pathway

P53 is a cancer suppressor gene which changes more than 50% of human cancers.⁴⁸ Cellular responses, such as cell cycle arrest, apoptosis, and metabolism adaptation, are induced by p53 under oxidative stress, undernutrition, oncogene activation, or DNA damage. P53 decreases glycolysis and increases mitochondrial respiration in energy metabolism and plays roles in nutrient metabolism, anti-oxidation, and apoptosis. Moreover, type 2 diabetes and life expectancy are related to p53 gene polymorphisms.⁷⁰ The function of p53 is related to metabolic disorders. For example, abnormally expressed p53 loses its tumor suppressor function but, conversely, gains carcinogenic function to promote tumor growth and interfere with cell metabolism.⁷¹ Therefore, p53 is crucial in various life activities, especially intracellular metabolism, cancer occurrence, and life expectancy.⁷²

Hepatitis C virus and hepatitis B virus infection in liver cancer tissues do not affect the expression of PLAC2, while the level of PLAC2 in non-cancerous tissues is significantly higher than that in HCC tissues. The higher the expression level of PLAC2 in liver cancer tissues, the higher the 5-year survival rate of patients and the better the prognosis. The expression of the *p53* gene is downregulated in liver cancer and is positively correlated with PLAC2. Low expression of PLAC2 leads to downregulation of p53 and reduces cancer cell apoptosis. In contrast, p53 overexpression does not affect PLAC2. In addition, p53 silencing reduces the impact of PLAC2 overexpression. Therefore, downregulation of PLAC2 can inhibit p53-mediated cancer cell apoptosis.⁴⁷ Overexpression of the *HOTAIR* gene can significantly increase the proliferation of MCF-7 cells and reduce apoptosis. The cell cycle arrest of *HOTAIR*-siRNA-transfected cells occurs in the G1 phase ($P < 0.01$). The high expression of *HOTAIR* leads to the proliferation of MCF-7 cells; migration and invasion abilities increase significantly, and the expression of Akt and JNK in MCF-7 cells also increased significantly ($P < 0.01$). However, the expression of p53 decreases significantly ($P < 0.01$). Therefore, silencing of the *HOTAIR* gene may reduce MCF-7 cell proliferation, increase apoptosis, inhibit migration, and inhibit invasion via regulation of the p53 signaling pathway.⁴⁸

The Role of lncRNAs in Autophagy

Autophagy is a mechanism that cells employ to promote organism survival under cell stress. The proteins and organelles in the lysosomes are captured, degraded, and recycled. Normal autophagy is required to maintain the function of organelles, reduce the toxic accumulation of cell waste, and provide substrates to maintain metabolism during starvation.⁷³ In most cases, autophagy promotes tumor occurrence, but in some cases, autophagy can inhibit tumor occurrence. Autophagy, which acts as a tumor-suppressing mechanism throughout early tumor formation, has a significant role in the survival of established tumor cells' reaction to cellular stress.⁷⁴ The regulation of cancer survival microenvironmental pressure, growth

promotion, and increased aggressiveness can be altered by upregulating autophagy. Tumor suppressor induction of p53 tumor suppressor protein and maintenance of mitochondrial metabolism can be accomplished by autophagy.⁷⁵ Autophagy is a highly conserved endosomal degradation system in eukaryotes. In the 1990s, the discovery of autophagy-related proteins accelerated the progress of autophagy research and clearly explained the important role of autophagy in various biological processes.⁷⁶ However, whether it plays a protective role in disease remains controversial. As cells age, autophagy gradually fades, manifested by the decrease in the formation of autophagic vacuoles, which are improperly fused with lysosomes.⁷⁷ Similarly, in neurodegenerative diseases, as autophagic clearance of proteins decreases, tau and synuclein proteins accumulate. The activation of more autophagy pathways also facilitates innate immunity to avoid various foreign pathogens. In the context of cancer, autophagy has been shown to play 2 opposite roles. It inhibits tumors in the initial stage, but later protects tumor cells from the immune system's defense mechanisms.⁷⁸ Our current understanding of autophagy can be roughly divided into 3 categories: macroautophagy, microautophagy, and partner-mediated autophagy. Macroscopic autophagy involves the degradation of lysosomal enzyme separation products: the isolation of cytoplasmic contents in the double-wall membrane, and then fusion with lysosomes. Microautophagy is the direct engulfment of cytoplasmic contents by lysosomes, while in partner-mediated autophagy, proteins specifically target lysosomes via signal peptides and coordinate through partners located on both sides of the targeting membrane.⁷⁹ One of the biggest concerns about treating cancer with autophagy is the potential effect on vital organs and normal cells. New ways to increase the effectiveness of cancer treatments are being experimented, and the good news is that they have cancer therapeutic potential.⁸⁰

The expression of DANCR in osteosarcoma tissues is significantly higher than that in normal tissues.⁸¹ Functional experiments show that upregulating DANCR can promote the proliferation, migration, invasion, and autophagy of osteosarcoma cells, but can inhibit cell apoptosis. In addition, this study also found that silencing the DANCR gene can inhibit the growth and autophagy of osteosarcoma.⁸² DANCR absorbs miR-216a-5p activity and regulates the survival of osteosarcoma by targeting miR-216a-5p.⁸³ In addition, miR-216a-5p can directly act on SOX and the silencing of miR-216a-5p promotes the expression of SOX.⁸⁴ Overexpressed lncRNA DANCR promotes the drugization process and autophagy of SOX5 in osteosarcoma by regulating miR-216a-5p, suggesting that DANCR may be a potential prognostic marker and therapeutic target of osteosarcoma.⁸³

SNHG11 is overexpressed in HCC cells. The "sponge" of miR-184 is SNHG11 and can directly act on AGO2. SNHG11 regulates AGO2 through miR-184 and promotes cell proliferation, migration, apoptosis, and autophagy. SNHG11 may provide a new biomarker for the diagnosis, treatment, and prognosis of HCC.⁸⁵

The expression of NEAT1 is associated with multiple tumors. The 5-year survival rate of patients with high expressions of NEAT1 in liver cancer tissues is low. Downregulating the expression of NEAT1 can promote the efficacy of sorafenib and inhibit autophagy. MicroRNA-204 (miR-204) may be mediated by NEAT1 and inhibit the expression of ATG3. Studies have found that miR-204 mimics can also attenuate tumor autophagy. Therefore, NEAT1 promotes HCC autophagy by regulating the miR-204/ATG3 pathway, which is the first proof that a new NEAT1/miR-204/ATG3 signal regulates the occurrence and development of liver cancer.⁸⁶

The Role of lncRNAs in Pyroptosis

The process of pyroptosis programs cells to induce inflammasomes. It was first described in 1992 when cells were infected by pathogens or bacteria. Pyroptosis is a new type of programmed inflammatory death, discovered after apoptosis and necrosis.⁸⁷ Similar to in apoptosis, pyroptotic cells undergo nuclear condensation and chromatin DNA fragmentation and become TUNEL-stain positive. Compared with necrosis, in the process of pyroptosis, the formation of pores disrupts the balance of ion gradients on both sides of the cell membrane, leading to water intake, cell swelling, cell membrane rupture, and release of proinflammatory mediators, including IL-1 β , IL-18, ATP, and HMGB1.⁸⁸ These mediators can induce inflammation, earning pyroptosis its alternative name: “inflammatory necrosis.” Pyroptosis is closely related to various human diseases, especially malignant tumors.⁸⁹ Pyroptosis may have 2 distinct roles in the pathogenesis of tumors. One is the stimulation of multiple signaling pathways and the release of multiple inflammatory mediators in the process of pyrolysis, which is closely related to the occurrence of tumors and its resistance to chemotherapy drugs. However, scorch death as a kind of death can inhibit the occurrence and development of tumors. With the deepening of research, the role of scorch death in tumors has been increasingly elucidated.^{90,91} Pyroptosis is connected to the clearing of various bacterial and viral infections by eliminating intracellular replication niches and increasing the host’s defensive responses.⁹² The correct pyrolysis pathway may increase pathogen clearance efficiency and promote adaptive immune stimulation. Researchers believe that inducing tumor pyroptosis may be a potential treatment strategy.⁹³

lncRNA GAS5 is downregulated in ovarian cancer tissues. Highly expressed lncRNA GAS5 leads to decreased cell proliferation and colony formation, and increased apoptosis in ovarian cancer cells. Conversely, low exogenous expression of lncRNA GAS5 can promote the proliferation, colony formation, and apoptosis of ovarian cancer cells. In addition, lncRNA GAS5 induces inflammasome formation, and pyrolysis induces the occurrence of ovarian cancer. Therefore, lncRNA GAS5 has a tumor suppressor effect and can be used as a potential target for the diagnosis and treatment of ovarian cancer.⁹⁴

NSCLC tissues and cell lines have been found to have abnormal overexpression of lncRNA-XIST. The influence of

downregulated lncRNA-XIST on ROS levels as well as pyroptotic cell death was found to be reversed by downregulated miR-335. Overall, pyroptotic cell death, which is mediated by targeting the miR-335/SOD2/ROS signaling pathway, is promoted by the downregulation of lncRNA-XIST and can be used to prevent NSCLC progression.⁹⁵

The Role of lncRNAs in Necrosis

Necrosis involves the abrupt loss of membrane completeness and the excretion of extracellular contents when the immune system and extensive inflammation are activated.⁹⁶ Traditionally, necrosis is regarded as an accidental and genetically unprogrammed form of cell death (programmed necrosis is known as “necroptosis”).⁹⁷ Necrosis is regarded as “repair cell death” in tumor progression and aggressiveness.⁹⁸ During necrosis, the cell swells, the cell membrane is ruptured, and the cytoplasmic content is released into the extracellular space. These contents include the high mobility group protein B1 (HMGB1) in the non-histone nucleoprotein, which can regulate gene expression and stabilize nucleosomes, and cause cell necrosis.⁹⁹ HMGB1 plays a role in promoting inflammation and tumor growth. These released cytoplasmic contents can recruit immune cells, thereby causing inflammation, increasing the probability of proto-oncogene mutations or epigenetic changes, inducing angiogenesis and cancer, and promoting tumor progression.¹⁰⁰ In the process of epithelial-mesenchymal transition (EMT), HMGB1 plays an important role, as it has the same functions as proinflammatory and protumor cytokines, thereby promoting tumor invasion and metastasis.^{101,102} These released molecules attract immune cells, which can arouse inflamed reactions and thus accelerate cancer progression by improving the chance of proto-oncogenic mutation or epigenetic transformation and promoting angiogenesis, proliferation of cancer cell, and invasiveness.^{103,104}

Under glucose starvation conditions, p53 directly upregulates a new lncRNA known as “TRINGS” (necrosis inhibitor regulated by Tp53 under glucose starvation conditions). TRINGS binds to trap, inhibits the trap-GSK3 β -NF- κ B necrosis signal, and protects tumor cells from cell death. Interestingly, TRINGS is particularly responsive to glucose deficiency because it is not activated by serum, serine, or glutamine deficiency. The findings of our previous study revealed that the p53-induced lncRNA chain controls the pathway of necrosis and contributes to the survival of cancer cells carrying wild-type p53 under glucose stress.⁴⁸

lncRNA plasmacytoma variant translocation 1 (PVT1) has been shown to be upregulated in human acute myeloid leukemia. Antisense LNA GapmeRs was used to block lncRNA PVT1 in a human acute erythrocyte leukemia (KG1) cell line, and lncRNA PVT1 could promote cell necrosis and apoptosis. Therefore, inhibition of lncRNA PVT1 can significantly induce apoptosis and necrosis in KG1 cells. The use of antisense therapy has broad prospects.¹⁰⁵

The Role of lncRNAs in Ferroptosis

Ferroptosis, which was first discovered in 2012 via chemical screening, is a newly named PCD process that features iron-dependent lipid peroxides accumulation. We elucidated the mechanism of ferroptosis based on the further research. We found that a train of small molecules was able to prompt ferroptosis in a variety of types of cancer cells.¹⁰⁶⁻¹⁰⁸ The morphological features associated with ferroptosis differ from those associated with other forms of regulated cell death. Compared with natural cells, the cells which progress by ferroptosis have smaller mitochondria, declining or disappearing mitochondria crista, and a ruptured mitochondrial membrane.¹⁰⁹ Adaptive features to eliminate the malignant cells are being gradually accepted by researchers about ferroptosis. Ferroptosis plays a vital role in tumorigenesis depression by clearing the cells that are short of primary nutrients or have suffered injury due to environmental or infection stress.¹¹⁰

lncRNA LINC00336 is upregulated in lung cancer and acts as an oncogene as a ceRNA. Ferroptosis is inhibited by the RNA binding protein ELAVL1 (ELAV-like RNA binding protein 1), which binds to LINC00336 to regulate the 1901-2107 nucleotides of LINC00336 and the RRM interaction domain and key amino acids of ELAVL1 (aa 101-213). The expression of LINC00336 is increased by ELAVL1, and ELAVL1 expression is increased by LSH (lymphoid-specific helicase) via the p53 signaling pathway, further supporting the hypothesis that LSH promotes the expression of LINC00336. The endogenous microRNA 6852 (MIR6852) sponge is LINC00336. Cystathionine- β -synthase (CBS) expression is regulated by LINC00336, which has a sponge-like effect on endogenous microRNA 6852 (MIR6852). This is a surrogate marker for ferroptosis and promotes the hypothesis that cell growth inhibition can be activated by MIR6852. This finding indicates that lncRNA and ceRNA play significant roles in tumorigenesis and ferroptosis.¹¹¹ The expression of lncRNAP53RRA is lower in cancer than in normal tissues, and plays an anticancer role by inhibiting tumor progression. 871 of P53RRA and Ras GTPase-activating protein-binding protein 1 (G3BP1) nucleotides 1 are bound to P53RRA. P53 is removed from the G3BP1 complex by the cytoplasmic P53RRA-G3BP1, leading to cell cycle arrest, ferroptosis, and apoptosis.¹¹² Ferroptosis and apoptosis are promoted by P53RRA via the exerting influence on the expression of metabolic genes.^{113,114} Therefore, lncRNA LINC00336 closely participate in ferroptosis in various cancer cells.^{111,114}

Conclusion

With the rapid development of cancer research, we will discover more about the treatment of cancer. Accumulating evidence has shown that the expression level of lncRNAs is closely related to different cell death modes and is related to the occurrence, metastasis, and prognosis of cancer. In this review, we have summarized the impact of lncRNAs on tumorigenesis among different death modes and the latest findings of

the regulatory role of lncRNAs in different signaling pathways in cancer pathogenesis.

lncRNAs have great potential as new diagnostic methods and prognostic indicators. Therefore, future challenges may focus on how to use lncRNAs to diagnose the occurrence of early cancer, and how to induce lncRNA expression in the body to promote the death of cancer cells through different death methods. The occurrence and development of tumors can be controlled by increasing or decreasing the expression of lncRNA. This method brings broad prospects for cancer treatment targeting lncRNA.

Authors' Note

This study did not require an ethical board approval because it did not contain human or animal trials.

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