Gene Expression **2025** vol. 000(000) | 000–000 Epub
DOI: 10.14218/GE.2024.00069

Review Article

Tumor Microenvironment Dynamics: The Regulatory Influence of Long Non-coding RNAs

Ozal Beylerli[1], Elmar Musaev[2], Chunlei Wang[3], Irina Popova[4,5] and Ilgiz Gareev[1*]

[1]*Central Research Laboratory, Bashkir State Medical University, Ufa, Republic of Bashkortostan, Russia;* [2]*Sechenov First Moscow State Medical University, Moscow, Russia;* [3]*Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China;* [4]*Medical Center of PJSC Novatek, Moscow, Russia;* [5]*Medical Center of LLC "Sherwood Premier", Moscow, Russia*

Received: December 03, 2024 | **Revised:** February 05, 2025 | **Accepted:** February 17, 2025 | **Published online:** February 22, 2025

Abstract

The tumor microenvironment (TME) consists of a complex mix of cellular and non-cellular components, including immune cells, stromal cells, extracellular matrix, cytokines, and growth factors. These elements interact with tumor cells to influence tumorigenesis, growth, invasion, and metastasis. Long noncoding RNAs (lncRNAs)—a class of non-coding RNAs longer than 200 nucleotides—have attracted considerable attention for their roles in regulating gene expression at the epigenetic, transcriptional, and post-transcriptional levels. Emerging evidence suggests that lncRNAs are crucial in shaping the TME by modulating processes such as immune evasion, angiogenesis, metabolic reprogramming, and the maintenance of cancer stem cells. This review provides an overview of the current understanding of lncRNAs in the TME, focusing on their involvement in key signaling pathways and cellular interactions that drive tumor progression. We discussed how lncRNAs contribute to extracellular matrix remodeling, facilitate communication between tumor and stromal cells, and regulate immune cell infiltration and function within the TME. Additionally, we explore the potential of lncRNAs as biomarkers for early cancer detection and prognosis, as well as their promise as therapeutic targets to disrupt tumor-microenvironment crosstalk. The review also addresses challenges in targeting lncRNAs therapeutically, such as ensuring specificity, minimizing off-target effects, and achieving effective *in vivo* delivery of lncRNA-targeted therapies. Strategies to overcome these challenges include the development of highly specific lncRNA knockout technologies and the use of advanced delivery systems, such as nanoparticles and viral vectors, to precisely target tumor-associated cells. Overall, this review underscores the significant role of lncRNAs in the TME and their potential as novel tools for enhancing cancer diagnosis and treatment. By elucidating the multifaceted roles of lncRNAs in the TME, we aimed to provide insights that could lead to more effective, targeted therapeutic strategies, ultimately advancing cancer research and improving patient care.

Introduction

The tumor microenvironment (TME) is a complex and dynamic network that plays a crucial role in shaping tumor behavior and influencing patient outcomes. It consists of tumor cells, tumor-associated fibroblasts, immune cells, vascular endothelial cells (ECs), signaling molecules, and the extracellular matrix (ECM).[1] These components interact in a way that promotes tumorigenesis, facilitates tumor progression, and drives metastasis.[2,3] Tumor cells continuously communicate with both non-tumor cells and non-cellular elements within the TME, adapting to various internal and external stimuli to maintain their malignant characteristics. Among the molecular regulators in the TME, long non-coding RNAs (lncRNAs) have emerged as key players. lncRNAs are RNA molecules longer than 200 nucleotides that do not code for proteins. They are categorized into five types based on their genomic location and orientation: sense, antisense, bidirectional, intronic, and intergenic lncRNAs.[4–7]

The discovery of tens of thousands of lncRNAs, which outnumber protein-coding genes, has generated significant interest due to their highly specific expression patterns across different cells, tissues, and tumors.[8–10] These unique expression profiles suggest that lncRNAs may have crucial roles in cellular processes and disease states, including cancer. Recent studies have revealed that lncRNAs are involved in a wide range of biological processes essential

Keywords: Tumor microenvironment; Long non-coding RNAs; Tumor progression; Tumor biomarkers; Therapeutic targets.

***Correspondence to:** Ilgiz Gareev, Central Research Laboratory, Bashkir State Medical University, 3 Lenin Street, Ufa, Republic of Bashkortostan 450008, Russia. ORCID: https://orcid.org/0000-0002-4965-0835. Tel: +7-937-4952927, E-mail: ilgiz_gareev@mail.ru

How to cite this article: Beylerli O, Musaev E, Wang C, Popova I, Gareev I. Tumor Microenvironment Dynamics: The Regulatory Influence of Long Non-coding RNAs. *Gene Expr* 2025;000(000):000–000. doi: 10.14218/GE.2024.00069.

for both normal cellular function and tumorigenesis, such as transcriptional activation and repression, gene imprinting, chromatin modification, and X chromosome inactivation.[11–13] lncRNAs can regulate gene expression at multiple levels—transcriptional, post-transcriptional, and translational—exerting profound effects on tumor development and progression. Unlike microRNAs (miRNAs), which typically repress gene expression, lncRNAs employ a variety of mechanisms to modulate cellular functions.[14,15] For instance, lncRNAs can directly interact with transcription factors to activate or suppress gene expression, or they can influence chromatin structure by recruiting chromatin remodeling complexes or serving as scaffolds for these complexes.[16–18] Some antisense lncRNAs also interact with complementary messenger RNAs (mRNAs) to regulate their splicing, translation, or degradation.[19] Beyond these roles, lncRNAs can alter protein localization, regulate protein activity, and participate in larger protein complexes.[20,21] Additionally, lncRNAs can function as competitive endogenous RNAs, sequestering miRNAs and thus regulating their availability to bind to target mRNAs.[22–24]

The role of lncRNAs in the TME is particularly compelling, as these molecules mediate the interactions between tumor cells and their surrounding environment. Through these interactions, lncRNAs contribute to essential processes such as promoting tumor growth, enhancing metastatic potential, inducing angiogenesis, conferring drug resistance, driving metabolic reprogramming, and facilitating immune evasion.[25–31] Given their involvement in these processes, lncRNAs have gained attention as potential molecular markers for cancer detection and as novel therapeutic targets. In this review, we aimed to synthesize current knowledge of lncRNAs within the TME, highlighting their diverse functions and potential applications in clinical oncology. We will explore how lncRNAs influence the TME and discuss how these insights may lead to new diagnostic tools and therapeutic strategies. By delving into the multifaceted roles of lncRNAs, this review seeks to lay the foundation for future research and underscore their promise as critical players in cancer biology.

lncRNAs and tumor microenvironment

Tumor cells constantly interact with their surrounding microenvironment during tumorigenesis and development.[32] They can influence this environment by secreting various signaling molecules, including lncRNAs.[33] These lncRNAs play a crucial role in promoting the proliferation, migration, angiogenesis, and immunosuppressive activities of surrounding non-tumor cells.[34–37] This dynamic interaction not only supports tumor growth and spread but also helps tumors evade immune detection.[38] Conversely, components within the tumor microenvironment—such as tumor-associated fibroblasts (TAFs), immune cells, and ECs—can also impact tumor cells and other non-tumor cells through lncRNAs.[39] These interactions can enhance tumor cell proliferation and migration, contribute to drug resistance, and facilitate further tumor progression.[40]

lncRNAs serve as mediators in these processes by influencing gene expression and cellular functions at multiple levels.[41] For example, lncRNAs secreted by tumor cells can bind to specific receptors on stromal cells, activating signaling pathways that alter the behavior of these cells.[42] In turn, these activated stromal cells produce factors that reinforce tumor cell growth and survival, creating a supportive feedback loop.[43] lncRNAs also modulate the immune response within the TME by affecting immune cell activity and infiltration. By promoting an immunosuppressive environment, lncRNAs help tumors evade immune detection and destruction.[38] Furthermore, lncRNAs regulate angiogenesis in the TME, which is crucial for providing tumors with the nutrients and oxygen necessary for rapid growth (Fig. 1).[36] lncRNAs achieve this by regulating angiogenic factors in both tumor cells and ECs. The dual role of lncRNAs in mediating interactions between tumor cells and their microenvironment highlights their significance in cancer biology.[39] These interactions are complex and multifaceted, involving not only direct cell-to-cell communication but also the alteration of the ECM and modulation of various signaling pathways.[35] Understanding the mechanisms by which lncRNAs orchestrate these interactions opens new avenues for therapeutic intervention.[44] Targeting specific lncRNAs that are critical for maintaining the TME could disrupt the supportive network that tumors rely on, potentially inhibiting tumor growth and progression.[34] Such an approach could also enhance the efficacy of existing treatments by reducing drug resistance and improving immune responses against the tumor.

In summary, lncRNAs are pivotal regulators in the intricate interplay between tumor cells and their microenvironment. By influencing the behavior of both tumor and non-tumor cells, they contribute to the dynamic nature of the TME and play key roles in tumor development and progression (Table 1).[45–47,54,55,59,82,83,87,88]

lncRNAs and TAFs

The relationship between TAFs and tumor cells within the TME is increasingly recognized as a critical factor in cancer progression and therapy resistance (Fig. 2). TAFs, the most abundant stromal cells in the TME, have a profound impact on tumor behavior by modulating various signaling pathways, often via lncRNAs.[45–50] These lncRNAs mediate the crosstalk between TAFs and tumor cells, contributing to a microenvironment that promotes tumor growth, invasion, and resistance to therapies (Fig. 3).

Transformation of fibroblasts into TAFs mediated by lncRNAs

A key aspect of TAF-tumor cell interaction is the role of lncRNAs in transforming normal fibroblasts into TAFs, significantly enhancing the pro-tumorigenic capabilities of the TME. For example, the lncRNA LOC100506114 is upregulated in TAFs associated with oral squamous cell carcinoma. This upregulation leads to increased expression and secretion of growth differentiation factor 10 by binding to the transcription factor RUNX2. RUNX2, in turn, drives the transformation of normal fibroblasts into TAFs, which actively promote the proliferation and migration of tumor cells.[45]

lncRNAs in tumor cell migration and invasion

lncRNAs also play a crucial role in tumor cell migration and invasion, key factors in cancer metastasis. The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which is overexpressed in various solid tumors, including ovarian epithelial carcinoma, exemplifies this role. MALAT1 overexpression in TAFs has been linked to enhanced migration of ovarian epithelial cells, indicating that lncRNAs can directly influence the invasive properties of tumor cells by altering the stromal compartment. This suggests that targeting lncRNAs like MALAT1 could disrupt the metastatic potential of cancer cells, offering a promising therapeutic strategy.[46]

lncRNAs and therapy resistance

TAFs also contribute to the development of resistance to various cancer therapies, a major obstacle in treating malignancies. The

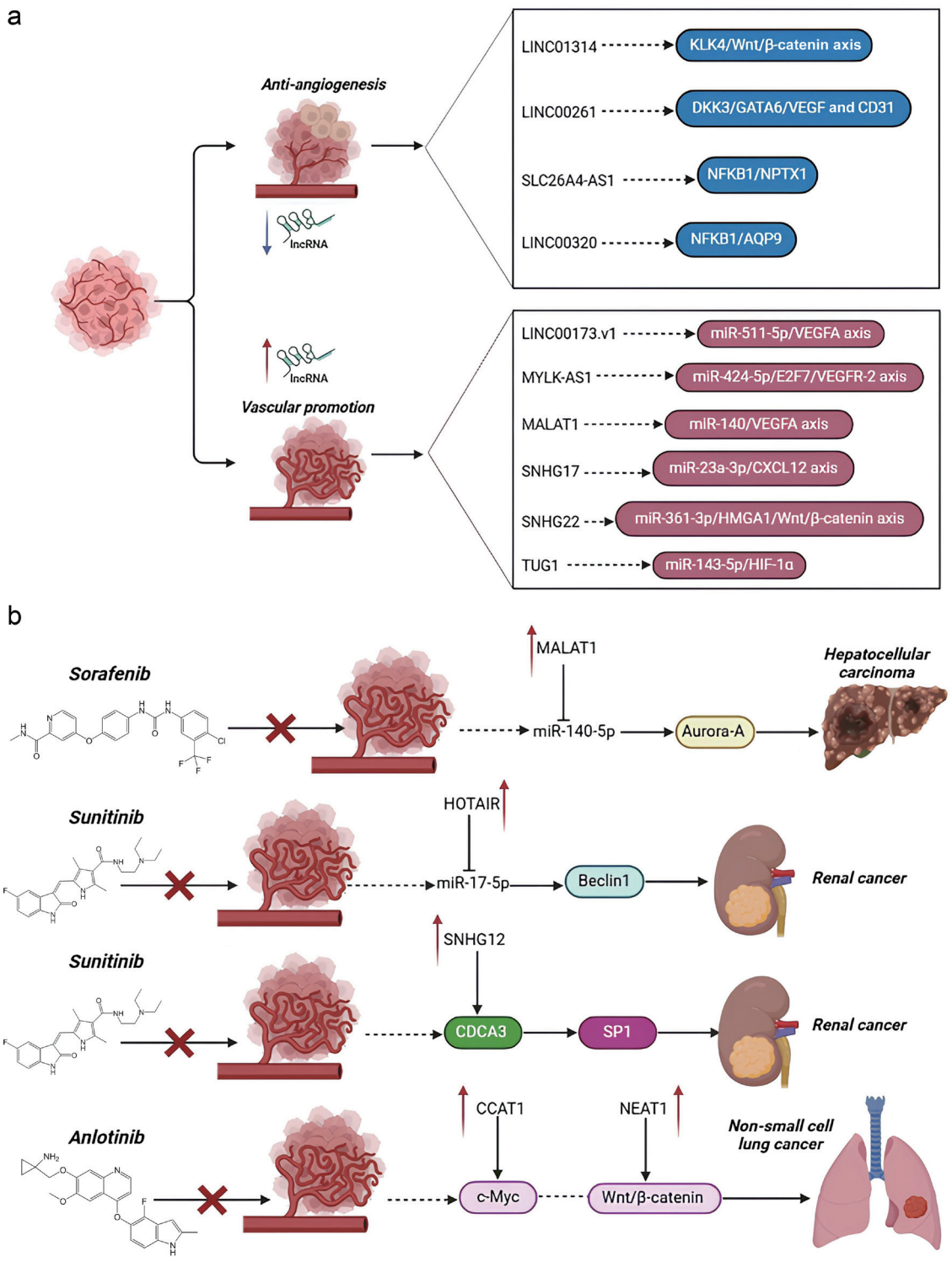

Fig. 1. Correlation between long non-coding RNAs (lncRNAs), angiogenesis, and anti-angiogenic therapy resistance in tumors. (a) Some lncRNAs have an anti-angiogenic effect, whereas others have a pro-angiogenic effect. (b) Some lncRNAs are closely related to anti-angiogenic therapy resistance, and lncRNAs are expected to be new targets for tumor therapy. AQP9, aquaporin-9; CD31, platelet/endothelial cell adhesion molecule 1; CDCA3, cell division cycle-associated protein 3; CXCL12, chemokine (C-X-C motif) ligand 12; DKK3, dickkopf-related protein 3; GATA6, GATA-binding factor 6; HIF-1α, hypoxia-inducible factor 1-alpha; KLK4, kallikrein related peptidase 4; NFKB1, nuclear factor of kappa light polypeptide gene enhancer in B-cells 1; NPTX1, neuronal pentraxin-1; SP1, specificity protein 1; VEGF, vascular endothelial growth factor; VEGFA, vascular endothelial growth factor A; VEGFR-2, vascular endothelial growth factor receptor 2.

Table 1. Roles of long noncoding RNAs (lncRNAs) in the tumor microenvironment

lncRNA	Tumor type	Role in tumor microenvironment	Mechanism	Ref.
LOC100506114	Oral squamous cell carcinoma	Transformation of fibroblasts to TAFs	Upregulates GDF10 expression via RUNX2, enhancing tumor cell proliferation and migration.	45
MALAT1	Ovarian cancer	Tumor cell migration and invasion	Overexpressed in TAFs promotes epithelial cell migration.	46
DNM3OS	Esophageal cancer	Radioresistance	Activates PDGFβ/PDGFRβ/FOXO1 pathway to enhance DNA damage response.	47
PVT1	Gastric cancer	Angiogenesis	Activates STAT3/VEGFA signaling axis, increasing VEGFA expression.	54
LINC00173.v1	Lung squamous cell carcinoma	Angiogenesis and chemoresistance	Acts as a sponge for miR-511-5p, enhancing VEGFA expression and endothelial cell proliferation.	55
HISLA	Breast cancer	Chemoresistance and aerobic glycolysis	Transferred via TAMs-derived exosomes; disrupts HIF-1α degradation, promoting anti-apoptosis and glycolysis.	59
CBSLR	Gastric cancer	Hypoxia adaptation	Interacts with YTHDF2, reduces mRNA stability of CBS, and prevents ferroptosis.	82
RAB11B-AS1	Breast cancer	Angiogenesis	Upregulated by HIF2, enhances transcription of VEGFA and ANGPTL4 under hypoxic conditions.	83
CRNDE	Gastric cancer	Promotes chemotherapy resistance and tumor growth	Transferred from M2-polarized macrophages via exosomes, promotes ubiquitination and degradation of PTEN, supports cancer cell survival and proliferation	87
LINC01614	Lung adenocarcinoma	Enhances metabolic support for tumor progression	Transferred from TAFs via exosomes, activates NF-κB signaling, upregulates glutamine transporters (SLC38A2 and SLC7A5), enhances glutamine metabolism	88

ANGPTL4, angiopoietin-related protein 4; CBS, cystathionine-β-synthase; FOXO1, forkhead box protein O1; GDF10, growth differentiation factor 10; HIF-1α, hypoxia-inducible factor 1-alpha; HIF2, hypoxia inducible factor 2; NF-κB, nuclear factor kappa B; PDGFRβ, platelet-derived growth factor receptor beta; PDGFβ, platelet-derived growth factor receptor beta; PTEN, phosphatase and tensin homolog deleted on chromosome 10; RUNX2, runx family transcription factor 2; SLC38A2, solute carrier family 38 member 2; SLC7A5, solute carrier family 7 member 5; STAT3, signal transducer and activator of transcription 3; TAFs, tumor-associated fibroblasts; TAMs, tumor-associated macrophages; VEGFA, vascular endothelial growth factor A; YTHDF2, YTH N6-methyladenosine RNA binding protein 2.

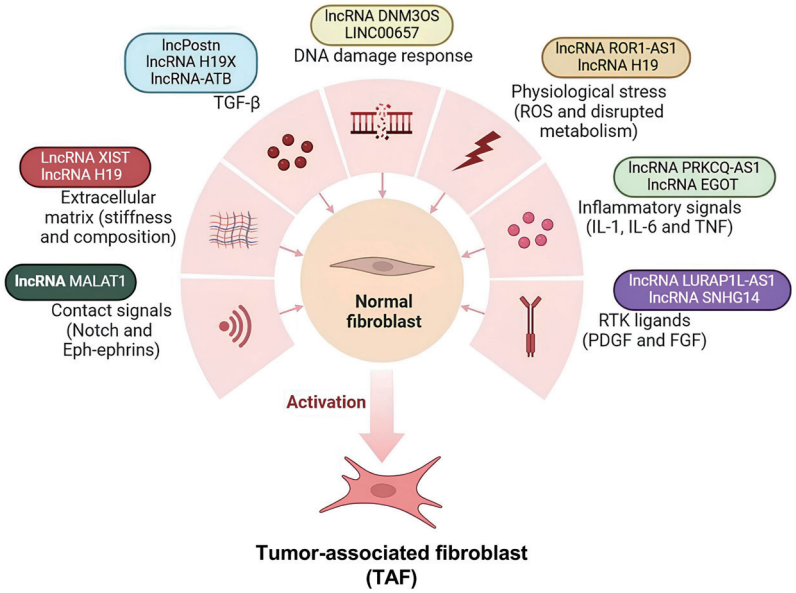

Fig. 2. Role of tumor-associated fibroblasts (TAFs) in tumor immunotherapy resistance. The process by which TAFs promote the formation of an immunosuppressive tumor microenvironment. FGF, fibroblast growth factor; PD-1, programmed cell death 1; IL, interleukin; lncRNA, long non-coding RNA; Notch, neurogenic locus notch homolog protein; PDGF, platelet-derived growth factor; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; RTK ligands, receptor tyrosine kinases; TNF, tumor necrosis factor.

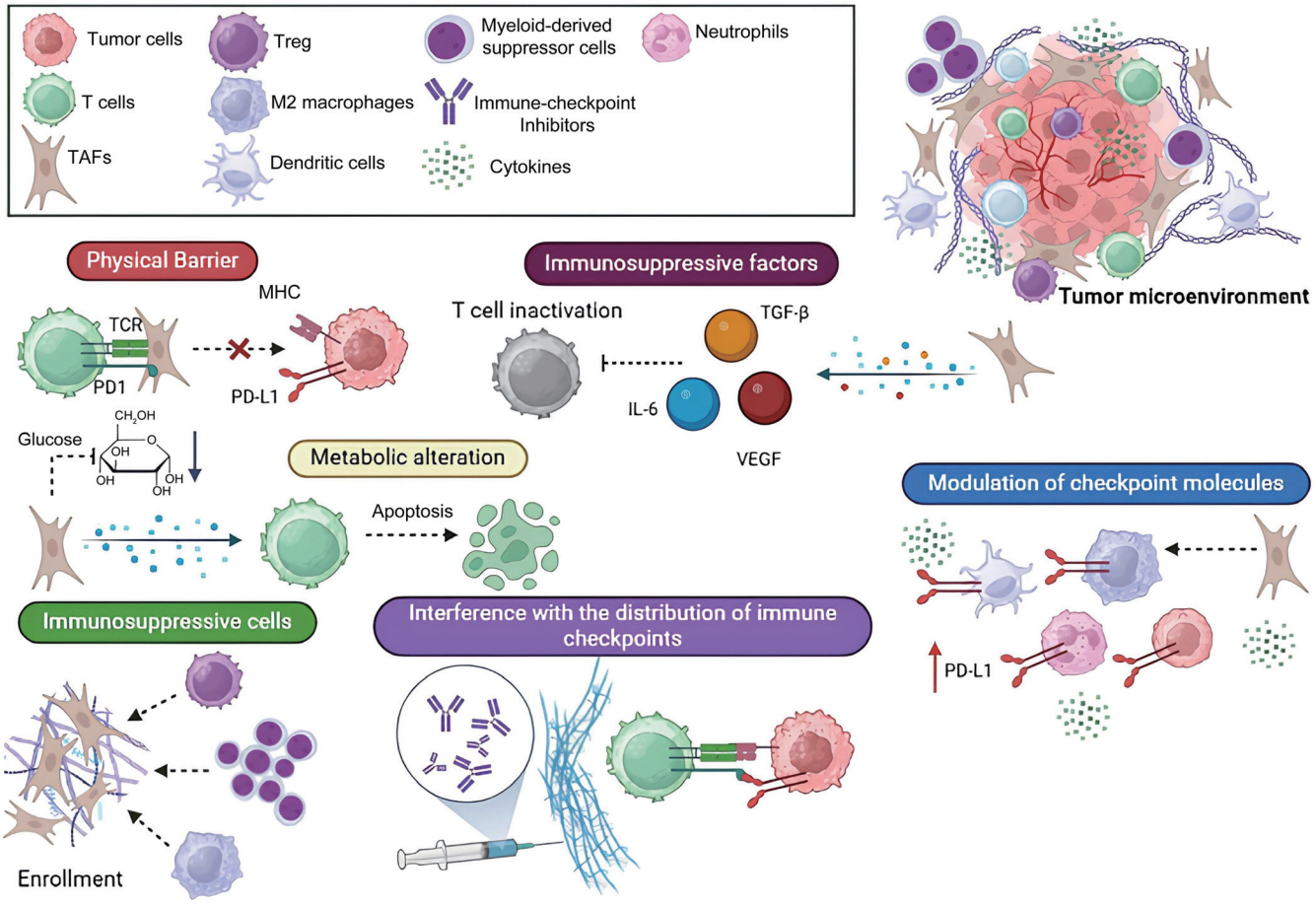

Fig. 3. Mechanisms of tumor-associated fibroblast (TAFs) activation by long non-coding RNAs (lncRNAs). TAFs, which promote tumor growth and metastasis, are the most important stromal components in the tumor microenvironment (TME). Meanwhile, TAFs are also important sources of many growth factors, chemokines, and cytokines such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), interleukin-6 (IL-6), and stromal cell-derived factor-1 (SDF-1). Some lncRNAs participate in the activation of normal fibroblasts to TAFs. Through lncRNAs, TAFs regulate tumor progression, including tumor cell proliferation, metabolism, immune escape, and treatment resistance. MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; Treg, regulatory T cells.

lncRNA dynamin 3 opposite strand is upregulated in esophageal cancer cells by TAFs through the platelet-derived growth factor β/platelet-derived growth factor receptor β/forkhead box O1 signaling pathway. Elevated expression of dynamin 3 opposite strand enhances resistance to radiotherapy by modulating the DNA damage response, a key mechanism by which cancer cells survive therapeutic interventions.[47] The heterogeneity of TAFs in the TME further complicates tumor behavior and response to treatment. In pancreatic cancer, particularly in patients with platinum-resistant disease, TAFs induce the overexpression of the lncRNA UPK1A-AS1 in tumor cells. This lncRNA promotes non-homologous end joining, a DNA repair pathway that allows pancreatic cancer cells to repair DNA double-strand breaks caused by chemotherapeutic agents like oxaliplatin. Notably, inhibiting UPK1A-AS1 expression *in vivo* sensitizes tumor cells to oxaliplatin, suggesting that targeting lncRNAs may overcome chemoresistance and improve patient outcomes.[50]

These findings highlight the multifaceted roles of lncRNAs in mediating interactions between TAFs and tumor cells and their broader impact on the TME. lncRNAs' ability to modulate key processes such as cell proliferation, migration, invasion, and therapy resistance makes them attractive targets for novel cancer therapies. By targeting specific lncRNAs, it may be possible to disrupt the supportive functions of TAFs, weakening the tumor's defenses and improving the efficacy of existing treatments. Furthermore, the exploration of lncRNAs in the TME opens new possibilities for biomarker discovery. Given their specific expression patterns across tumor types and their involvement in critical tumor-promoting processes, lncRNAs could serve as valuable biomarkers for early diagnosis, prognosis, and monitoring of treatment responses. Integrating lncRNA profiling into clinical practice could enhance cancer management precision, enabling more personalized and effective therapeutic strategies.

lncRNAs and endothelial cells

Within the TME, vascular ECs play a crucial role in the formation of new blood vessels—a process known as angiogenesis—that supports tumorigenesis, growth, invasion, and metastasis. The activation of these ECs is essential for providing the tumor with the nutrients and oxygen it needs to expand and spread. Recent

studies have highlighted that lncRNAs are key regulators of EC activation, significantly contributing to the angiogenic process in various cancers.[51–55]

In breast cancer, the lncRNA NR2F1-AS1 is positively correlated with the expression of EC markers CD31 and CD34, which are indicators of angiogenesis. NR2F1-AS1 enhances the expression of insulin-like growth factor-1 (IGF-1) in breast cancer cells by binding to miRNA-338-3p. This increase in IGF-1 activates the IGF-1 receptor and the extracellular signal-regulated kinase pathways in human umbilical vein endothelial cells, leading to enhanced EC proliferation, tube formation, and migration.[53] This mechanism underscores NR2F1-AS1's role in driving the angiogenic switch, which is essential for breast cancer progression.

Similarly, in gastric cancer, the lncRNA plasmacytoma variant translocation 1 (PVT1) is significantly upregulated and has been shown to promote tumor angiogenesis by activating the signal transducer and activator of transcription 3/vascular endothelial growth factor A (VEGFA) signaling axis. Upregulation of PVT1 increases VEGFA expression, a key driver of new blood vessel formation, thereby aiding tumor growth and metastasis.[54] This suggests that PVT1 plays a crucial role in modulating the angiogenic potential of gastric tumors, positioning it as a potential target for therapeutic intervention.

In lung squamous cell carcinoma, the lncRNA LINC00173.v1 is specifically upregulated, and its overexpression has been linked to increased angiogenesis. LINC00173.v1 acts as a molecular sponge for miR-511-5p, thereby promoting VEGFA expression. This upregulation enhances EC proliferation and migration, further contributing to tumor progression. Notably, targeting LINC00173.v1 with antisense oligonucleotides (ASOs) has been shown to reduce tumor growth and increase the sensitivity of lung squamous cell carcinoma cells to cisplatin, a chemotherapy drug.[55] This finding underscores the therapeutic potential of targeting specific lncRNAs to disrupt the angiogenic processes that tumors rely on for survival and resistance to treatment.

Together, these studies highlight that lncRNAs are not only involved in regulating EC function but also act as key drivers of angiogenesis, a process essential for tumor development and metastasis. By modulating signaling pathways such as IGF-1 receptor/extracellular signal-regulated kinase, signal transducer and activator of transcription 3A/VEGFA, and miR-511-5p/VEGFA, lncRNAs like NR2F1-AS1, PVT1, and LINC00173.v1 play pivotal roles in the activation and behavior of vascular ECs within the TME. The potential of lncRNAs as therapeutic targets is particularly evident in their ability to modulate angiogenesis. Inhibiting specific lncRNAs, as shown with LINC00173.v1, can impair tumor growth by disrupting blood supply and enhance the effectiveness of conventional therapies like chemotherapy. Therefore, lncRNAs present a promising avenue for developing novel anti-angiogenic therapies that could complement existing treatment options, offering new hope for patients with aggressive, treatment-resistant cancers. The role of lncRNAs in promoting EC activation and angiogenesis within the TME is a critical aspect of tumor biology. As our understanding of these molecular mechanisms deepens, targeting lncRNAs may provide a powerful strategy for inhibiting tumor progression and improving the efficacy of cancer treatments. Further research into lncRNA-mediated pathways is expected to offer valuable insights into the development of next-generation cancer therapies.

lncRNAs and tumor-associated immune cells

Within the TME, tumor-associated macrophages (TAMs) are the most abundant inflammatory cells, and their presence is strongly correlated with poor prognosis in various cancers.[56] TAM plays a crucial role in enhancing tumor malignancy by modulating the expression of lncRNAs in tumor cells. This modulation affects critical cellular processes such as proliferation, motility, invasiveness, and resistance to chemotherapy, driving tumor progression.[57–59] Understanding the specific lncRNAs involved in TAM-tumor cell interactions is vital for developing targeted therapies aimed at disrupting these pro-tumorigenic pathways.

lncRNA HISLA

A key mechanism through which TAMs influence tumor cells is by transferring specific lncRNAs via extracellular vesicles. In breast cancer, TAMs have been found to transfer the lncRNA HISLA (hypoxia-induced lncRNA associated) to tumor cells through these vesicles. Inside the tumor cells, HISLA disrupts the interaction between prolyl hydroxylase domain protein 2 and hypoxia-inducible factor (HIF)-1 alpha. This disruption inhibits the hydroxylation and degradation of hypoxia-inducible factor-1 beta, leading to enhanced aerobic glycolysis and increased anti-apoptotic capabilities in the tumor cells. Interestingly, the lactic acid produced during glycolysis by tumor cells further upregulates HISLA expression in macrophages, creating a positive feedback loop between TAMs and tumor cells. This loop not only sustains tumor malignancy but also promotes chemoresistance. Inhibiting HISLA transfer through extracellular vesicles has been shown to reduce glycolysis and chemoresistance in breast cancer cells, highlighting the therapeutic potential of targeting lncRNA-mediated pathways.[58]

lncRNA ribonuclease P RNA component H1 (RPPH1)

TAMs exhibit functional heterogeneity and can be classified into two main subsets: M1 and M2 macrophages. M1 macrophages are typically associated with antitumor activity, while M2 macrophages promote tumor progression. Tumor cells can manipulate TAM differentiation into these subsets via lncRNAs. In colorectal cancer, the lncRNA RPPH1 is significantly upregulated in tumor tissues. RPPH1 promotes epithelial-mesenchymal transition (EMT) in colorectal cancer cells by interacting with β-tubulin III, a key protein involved in cell motility and stability. Additionally, colorectal cancer cells can package RPPH1 into exosomes, which are then transferred to macrophages. Inside the macrophages, RPPH1 influences their polarization, driving them toward an M2-like, protumor phenotype. This polarization supports the proliferation and metastasis of colorectal cancer cells and contributes to the overall pro-tumorigenic environment in the TME.[59]

These findings underscore the complex interplay between TAMs and tumor cells, mediated by lncRNAs, within the TME. lncRNAs like HISLA and RPPH1 regulate critical processes such as glycolysis, apoptosis, EMT, and macrophage polarization, emphasizing their importance in tumor biology. By facilitating communication between tumor cells and TAMs, these lncRNAs contribute to a microenvironment that promotes tumor growth, metastasis, and therapy resistance. Given the central role of lncRNAs in these processes, they represent promising therapeutic targets. Disrupting the transfer of HISLA or inhibiting the expression of RPPH1 could impair TAM functions, weakening tumor defenses and enhancing the efficacy of existing treatments. Moreover, targeting lncRNA-mediated signaling pathways may offer a strategy to reprogram TAMs from a protumor M2 phenotype to an antitumor M1 phenotype, further promoting tumor suppression.

lncRNAs and T cells

T cells are essential components of the adaptive immune response

against tumors, but their efficacy is often compromised within the TME through various mechanisms regulated by lncRNAs. The lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) has been shown to modulate the expression of immune checkpoint molecules such as programmed death (PD)-ligand 1 on tumor cells. By upregulating PD-ligand 1, NEAT1 inhibits cytotoxic T cell activity, enabling tumor cells to escape immune surveillance.[60] Similarly, the lncRNA MALAT1 interacts with miRNAs to influence PD-1 expression on T cells. Elevated MALAT1 levels correlate with increased PD-1 expression, leading to T cell exhaustion and reduced anti-tumor immunity.[61] lncRNA Taurine upregulated gene 1 (TUG1) regulates the expression of CTLA-4 on T cells. By enhancing CTLA-4 expression, TUG1 suppresses T cell activation and proliferation, promoting immune tolerance in the TME.[62] lncRNA Theiler's murine encephalomyelitis virus persistence gene 1/NeST is involved in the differentiation of $CD8^+$ T cells into effector cells. Dysregulation of PD1Hi $CD8^+$ T cells impairs their cytotoxic function, reducing their ability to target and eliminate tumor cells effectively.[63] Overexpression of LINC00473 in tumor cells has been linked to the suppression of Th1-type immune responses, mediated by cytokine production, resulting in a less effective T cell-mediated anti-tumor response.[64] lncRNA interferon-gamma (IFN-γ) antisense RNA 1 enhances the production of IFN-γ in T cells. Downregulation of IFN-γ antisense RNA 1 in the TME can lead to reduced IFN-γ levels, weakening the Th1 immune response and facilitating immune evasion by the tumor.[65] The lncRNA Urothelial carcinoma-associated 1 (UCA1) influences T cell metabolism, altering glucose metabolism to reduce T cell proliferation and effector functions, further contributing to an immunosuppressive TME.[66] lncRNA Growth arrest-specific 5 (GAS5) regulates the mammalian target of rapamycin signaling pathway in T cells. Reduced GAS5 levels lead to hyperactivation of mammalian target of rapamycin, impairing T cell differentiation and function.[67] Finally, lncRNA small nucleolar RNA host gene 16 modulates the expression of chemokines that influence T cell migration into the tumor site. Elevated small nucleolar RNA host gene 16 levels are associated with reduced T cell infiltration, limiting the immune system's ability to target tumor cells effectively.[68]

lncRNAs and natural killer (NK) cells

NK cells are essential for the innate immune response against tumors, capable of recognizing and killing tumor cells without prior sensitization. However, their activity can be hindered within the TME through lncRNA-mediated mechanisms. One such lncRNA, NK cell inhibitory ligand-associated lncRNA, is upregulated in certain tumors and interacts with signaling pathways that suppress NK cell activation. This inhibition reduces NK cell cytotoxicity against tumor cells, facilitating immune evasion.[69] lncRNA MIR155HG not only affects NK cell maturation but also modulates the expression of activating receptors on NK cells. Abnormal expression of MIR155HG can lead to reduced levels of receptors like natural killer group 2D, which diminishes NK cell-mediated cytotoxicity.[70] Similarly, lncRNA GAS5, in addition to its role in T cells, regulates the production of cytokines such as IFN-γ in NK cells. Downregulation of GAS5 in the TME leads to decreased IFN-γ secretion, impairing NK cell function and hindering anti-tumor responses.[71] lncRNA deleted in lymphocytic leukemia 1 enhances the production of immunosuppressive cytokines, such as TGF-β, in NK cells. Elevated deleted in lymphocytic leukemia 1 levels contribute to a suppressed NK cell phenotype, reducing their anti-tumor efficacy.[72] Beyond its role in inhibiting NK cell activation, MIR155HG also plays a critical role in NK cell maturation. Disruption of its expression can impair normal NK cell development, leading to a reduced population of functional NK cells within the TME.[73] lncRNA RPPH1, like its effect on macrophage polarization, can also influence NK cell maturation by modulating the expression of transcription factors essential for NK cell development.[74] Additionally, lncRNA HOX transcript antisense RNA (HOTAIR) alters the metabolic state of NK cells by modulating mitochondrial function. Enhanced expression of HOTAIR leads to mitochondrial dysfunction, decreasing NK cell viability and cytotoxicity.[75]

lncRNAs and other immune cells

Beyond T cells and NK cells, lncRNAs also interact with other immune cells within the TME, such as dendritic cells (DCs) and myeloid-derived suppressor cells (MDSCs), further contributing to immune modulation. lncRNA HOXA transcript antisense RNA myeloid-specific 1 regulates the maturation and antigen-presenting capacity of DCs. Downregulation of HOXA transcript antisense RNA myeloid-specific 1 impairs DC function, reducing their ability to activate T cells and initiate an effective immune response.[76] lncRNA DC-specific transcript 1 antisense RNA 1 enhances the expression of co-stimulatory molecules on DCs, promoting T cell activation. Tumors may downregulate DC-specific transcript 1 antisense RNA 1 to evade immune detection.[77] lncRNA RUNX family transcriptional regulator OR (RUNXOR) is involved in the expansion and immunosuppressive function of MDSCs. Elevated RUNXOR levels promote MDSC accumulation in the TME, enhancing their ability to suppress T cell activity.[78] Similarly, lncRNA small nucleolar RNA host gene 1 facilitates the recruitment and activation of MDSCs by upregulating chemokines and immunosuppressive factors, thereby creating an immunosuppressive TME that supports tumor growth.[79]

The roles of lncRNAs in regulating various immune cells within the TME present novel therapeutic opportunities. Modulating lncRNAs such as NEAT1, MALAT1, and TUG1 could enhance the efficacy of immune checkpoint inhibitors by restoring T cell activity and overcoming tumor-induced immune suppression. Strategies aimed at increasing the expression of lncRNAs that promote T cell and NK cell activation, such as Theiler's murine encephalomyelitis virus persistence gene 1/NeST or GAS5, could enhance the immune system's ability to combat tumors. Inhibiting lncRNAs like RUNXOR and small nucleolar RNA host gene 1 could reduce the immunosuppressive functions of MDSCs and improve the antigen-presenting capabilities of DCs, thus boosting immune surveillance. Targeting lncRNAs that alter the metabolic pathways of T and NK cells, such as UCA1 and HOTAIR, could restore the metabolic fitness and functionality of these immune cells within the TME. Combining lncRNA-targeted therapies with existing treatments, such as chemotherapy, radiotherapy, and immunotherapy, may result in synergistic effects, improving treatment outcomes and overcoming resistance mechanisms.

The interplay between lncRNAs and various tumor-associated immune cells, including TAMs, T cells, NK cells, DCs, and MDSCs, underscores the multifaceted role of lncRNAs in tumor biology. By orchestrating complex signaling networks that regulate immune cell function, lncRNAs contribute to create an immunosuppressive TME that supports tumor growth and resistance to therapy. As research uncovers the diverse functions of lncRNAs, these molecules hold significant promise as targets for innovative cancer therapies aimed at modulating the immune landscape within tumors. Comprehensive understanding and targeted manipulation of lncRNAs-mediated pathways could enhance immune sur-

veillance, slow tumor progression, and improve clinical outcomes for cancer patients.

lncRNAs and the hypoxic tumor microenvironment

Hypoxia is a hallmark of the TME.[80] In many cancers, including breast and gastric cancers, tumor cells exhibit high metabolic activity, leading to increased oxygen consumption. Combined with the presence of abnormal blood vessels, this results in insufficient oxygen supply to the tumor cells. In response to these low-oxygen conditions, a range of genes, including lncRNAs, are dysregulated, driving tumor progression and metastasis.[81–83]

A key discovery in this context is the hypoxia-induced overexpression of the lncRNA CBSLR in gastric cancer cells. Under hypoxic conditions, CBSLR interacts with the RNA-binding protein YTH N6-methyladenosine RNA binding protein 2 (YTHDF2), forming a CBSLR/YTHDF2/cystathionine-β-synthase (CBS) signaling axis. This axis plays a critical role in modulating mRNA stability by enhancing the N6-methyladenosine modification of YTHDF2 and CBS mRNA. This modification reduces the stability of CBS mRNA, leading to the degradation of acyl-CoA synthetase long-chain family member 4, a key enzyme in lipid metabolism. The degradation of acyl-CoA synthetase long-chain family member 4 prevents ferroptosis, a form of programmed cell death driven by iron and lipid peroxidation, thereby promoting the survival and malignancy of gastric cancer cells under hypoxic stress.[82]

In addition to the CBSLR/YTHDF2/CBS axis, hypoxia also regulates the expression of other lncRNAs through the action of HIFs. HIFs are transcription factors that become stabilized and active in low-oxygen conditions, driving the transcription of genes that help tumors adapt to hypoxia. For example, in breast cancer, HIF2 has been shown to upregulate the expression of lncRNA RAB11B-AS1. This lncRNA enhances the recruitment and activity of RNA polymerase II, which in turn increases the transcription of key angiogenic factors such as VEGFA and angiopoietin-like 4. The overexpression of these factors promotes angiogenesis—the formation of new blood vessels—which is essential for supplying growing tumors with nutrients and oxygen. Moreover, angiogenesis facilitates distant metastasis by providing tumor cells access to the circulatory system, allowing them to spread to other parts of the body.[83]

These findings underscore the critical role of lncRNAs in helping tumor cells adapt to the hypoxic conditions within the TME. By modulating various signaling pathways and gene expression programs, lncRNAs such as CBSLR and RAB11B-AS1 enable tumor cells to survive, grow, and metastasize in this challenging environment. This adaptation not only supports tumor progression but also poses significant challenges for treatment, as hypoxia-driven changes can contribute to therapy resistance and tumor aggressiveness. The intricate relationship between hypoxia and lncRNA expression highlights the potential for targeting these molecules therapeutically. Disrupting hypoxia-induced signaling pathways mediated by lncRNAs may hinder tumor adaptation to low-oxygen conditions, reducing tumor growth and preventing metastasis. Additionally, targeting lncRNAs involved in hypoxia responses could enhance the effectiveness of existing therapies, particularly in tumors where hypoxia plays a major role in progression and resistance.

lncRNAs and exosomes

Exosomes play a pivotal role in intercellular communication within the TME, with lncRNAs encapsulated in these vesicles serving as key mediators of this interaction. Exosomes are lipid bilayer vesicles ranging from 40 to 150 nm in diameter, capable of transporting a variety of molecular components, including proteins, DNA, mRNA, lncRNAs, and miRNAs. Nearly all eukaryotic cells can secrete exosomes, making them valuable as molecular markers and drug delivery vehicles for disease diagnosis and therapy.[84,85] In the TME, lncRNAs are selectively packaged into exosomes, facilitating communication between tumor cells and surrounding stromal cells. This transfer of lncRNAs plays an essential role in regulating tumor biology, including angiogenesis, tumor growth, metastasis, and chemotherapy resistance.[86–88] A notable example is the lncRNA CRNDE, which is upregulated in both tumor tissues and TAMs in gastric cancer.

CRNDE is transferred from M2-polarized macrophages to gastric cancer cells via exosomes. Once inside the cancer cells, CRNDE promotes the ubiquitination of phosphatase and tensin homolog by neural precursor cell-expressed developmentally downregulated protein 4-1. This ubiquitination leads to the degradation of phosphatase and tensin homolog, a crucial tumor suppressor, supporting cancer cell survival and proliferation. Notably, silencing CRNDE in these M2-derived exosomes has been shown to reverse the proliferative effects of cisplatin on gastric cancer cells and inhibit tumor growth in cisplatin-treated nude mice xenograft models.[87]

This example highlights the dual role of lncRNAs in promoting tumor progression and conferring chemotherapy resistance. By mediating the transfer of lncRNAs like CRNDE through exosomes, TAMs contribute to a more aggressive and treatment-resistant cancer phenotype. Targeting these exosomal lncRNAs offers a promising therapeutic strategy to disrupt supportive interactions within the TME, thereby enhancing the efficacy of existing cancer treatments and improving patient outcomes.

The selective packaging of lncRNAs into exosomes and their transfer between cells within the TME emphasize their potential as both therapeutic targets and diagnostic biomarkers. Targeting exosomal lncRNAs could disrupt pro-tumorigenic communication pathways, reducing tumor growth, metastasis, and therapy resistance. Additionally, the presence of specific lncRNAs within circulating exosomes offers a minimally invasive approach to cancer diagnosis and monitoring of treatment responses, enabling more personalized and timely therapeutic interventions.

In lung adenocarcinoma, TAFs similarly modulate tumor progression through the exosomal delivery of lncRNAs. Specifically, TAFs have been found to transfer lncRNA LINC01614 to lung cancer cells via exosomes. Once delivered, LINC01614 directly interacts with AXNA2 and p65, components of the NF-κB signaling pathway. This interaction activates NF-κB, which upregulates the expression of glutamine transporters solute carrier family 38 member 2 and solute carrier family 7 member 5. These transporters enhance glutamine metabolism in lung cancer cells, supporting rapid growth and proliferation. By promoting these metabolic pathways, LINC01614 contributes to the progression of lung adenocarcinoma.[88] The ability of exosomes to protect and transport lncRNAs like CRNDE and LINC01614 within the TME underscores their significance in tumor progression. The lipid bilayer of exosomes ensures that these lncRNAs remain stable and functional as they move between different cell types within the tumor, exerting their effects on various aspects of tumor biology. This stability not only facilitates communication between different cell populations in the TME but also allows for the precise regulation of processes such as cell proliferation, survival, and therapy resistance.

The growing understanding of exosome-mediated lncRNA transfer in cancer reveals their potential for clinical applications. By targeting specific lncRNAs within exosomes, it may be possible to disrupt the pathological communication networks in the TME, inhibiting tumor growth and overcoming resistance to treatments. Moreover, exosomes themselves offer a promising platform for delivering therapeutic agents, including lncRNA-based therapies, directly to tumor cells, potentially enhancing treatment specificity and efficacy.

Exosomes play a pivotal role in the TME by serving as vehicles for lncRNAs that regulate key processes in tumor progression, such as glucose metabolism, proliferation, and chemoresistance (Figs. 4–6). The protective nature of the exosomal lipid bilayer enables stable delivery of lncRNAs to various cells within the TME, amplifying their impact on tumor development. As research advances, exosome-mediated lncRNA transfer presents a promising avenue for innovative cancer therapies and diagnostic tools.

Clinical application value of lncRNAs in the tumor microenvironment

The abnormal expression of lncRNAs within the TME plays a crucial role in influencing tumor growth and progression. As research into the functions and mechanisms of lncRNAs in the TME has advanced, these molecules have emerged as valuable molecular markers for early cancer detection and as promising targets for therapeutic interventions.[89–92] lncRNAs, which regulate various cellular processes, are increasingly recognized for their ability to modulate the behavior of both tumor cells and surrounding stromal cells within the TME. Dysregulation of specific lncRNAs can enhance tumorigenic properties, such as increased proliferation, invasion, and resistance to apoptosis. These aberrant expression patterns are typically not random but closely tied to the specific characteristics and stages of tumor progression.

One of the most promising aspects of lncRNAs is their potential as biomarkers for early cancer diagnosis. Unlike traditional protein markers, lncRNAs are often more specific to certain cancer types and can be detected in body fluids such as blood or urine, making them ideal for non-invasive diagnostic tests.[93–95] For instance, circulating lncRNA HOTAIR has been identified as a promising biomarker for the early detection of colorectal cancer, with elevated levels found in the plasma of affected individuals compared to healthy controls.[96] Similarly, lncRNA PCA3 is used as a urinary biomarker for prostate cancer, offering higher specificity and sensitivity than the conventional prostate-specific antigen test.[97]

Early detection is crucial for improving patient outcomes, as it enables timely treatment initiation, which is often more effective in the early stages of cancer. Additionally, the identification of lncRNAs as therapeutic targets opens up new avenues for cancer treatment. Targeting lncRNAs that are overexpressed in the TME could disrupt the supportive interactions between tumor cells and their environment, inhibiting tumor growth and reducing the likelihood of metastasis. Potential therapeutic strategies include the use of antisense oligonucleotides, small interfering RNAs (siRNAs), or small molecules designed to specifically inhibit the function of oncogenic lncRNAs. Furthermore, lncRNAs that are downregulated in tumors could be targeted for reactivation, potentially restoring their tumor-suppressive functions.

Ongoing research into lncRNAs in the TME is also uncovering their role in mediating resistance to conventional therapies.[98] Some lncRNAs are involved in regulating drug efflux pumps, DNA repair mechanisms, or apoptotic pathways, contributing to a tumor's resistance to chemotherapy, radiotherapy, or targeted therapies. By targeting these lncRNAs, it may be possible to sensitize tumors to existing treatments, enhancing their efficacy and overcoming resistance.

For example, UCA1 enhances the expression of the drug efflux pump ABCB1 in breast cancer cells, leading to increased resistance to doxorubicin. Silencing lncRNA UCA1 has been shown to reduce ABCB1 expression and restore doxorubicin sensitivity in breast cancer models.[99] NEAT1 facilitates DNA repair in ovarian cancer cells by interacting with BRCA1, contributing to resistance against poly(ADP-ribose) polymerase inhibitors. Inhibition of NEAT1 expression enhances the efficacy of poly(ADP-ribose) polymerase inhibitors in ovarian cancer by impairing DNA repair mechanisms.[100] HOTAIR inhibits apoptosis in hepatocellular carcinoma cells by modulating the expression of B-cell lymphoma-2 family proteins, contributing to resistance against cisplatin treatment. Targeting lncRNA HOTAIR can restore apoptotic pathways and sensitize cancer cells to cisplatin.[101]

These findings highlight the growing importance of lncRNAs as biomarkers in cancer diagnostics. Their stability in body fluids and strong association with tumor characteristics make them valuable candidates for the development of non-invasive diagnostic tests. As research progresses, integrating lncRNA-based biomarkers into clinical practice could revolutionize early cancer detection, leading to earlier interventions and improved prognoses for patients (Table 2).[55,87,94–98,102–105]

Clinical application of lncRNAs in tumor therapy

The complex nature of the TME has made it clear that therapies focused solely on targeting tumor cells are often insufficient for effective cancer treatment. Recent studies have highlighted the potential of lncRNAs within the TME as both molecular markers for predicting tumor prognosis and as promising targets for therapeutic intervention.[99,100] This shift in focus has spurred the development of innovative treatment strategies that utilize technologies such as siRNA, ASOs, CRISPR, and locked nucleic acid to specifically target lncRNAs within the TME.[101,102]

For instance, in cases of sunitinib-resistant advanced renal cell carcinoma, the lncRNA lncARSR contributes to drug resistance by promoting the expression of AXL and c-MET through competitive binding with miR-34/miR-449. This lncRNA can be packaged into exosomes and transferred to other cells, spreading resistance to sunitinib among tumor cells. Targeting lncARSR with locked nucleic acid technology in mouse models has proven effective in delaying the progression of sunitinib-resistant renal cell carcinoma and restoring the tumors' sensitivity to the drug.[103]

In colorectal cancer, the lncRNA FLANC is significantly overexpressed and plays a role in promoting metastasis. High levels of FLANC are linked to poor patient prognosis. Researchers have demonstrated that using nanovesicles to deliver siRNAs targeting FLANC can effectively inhibit tumor growth and metastasis in mouse models, providing a potential therapeutic approach for colorectal cancer.[104]

The lncRNA PKMYT1AR, highly expressed in non-small cell lung cancer, plays a crucial role in maintaining cancer stem cells by regulating the PKMYT1AR/miR-485-5p/PKMYT1 axis, which inhibits the ubiquitin-mediated degradation of β-catenin by β-TrCP1. Targeting PKMYT1AR with ASOs has significantly reduced tumor growth in mouse models, demonstrating the potential of lncRNA-targeted therapies in cancer treatment.[105]

These examples underscore the potential of targeting lncRNAs in the TME, not only to reverse drug resistance but also to inhibit

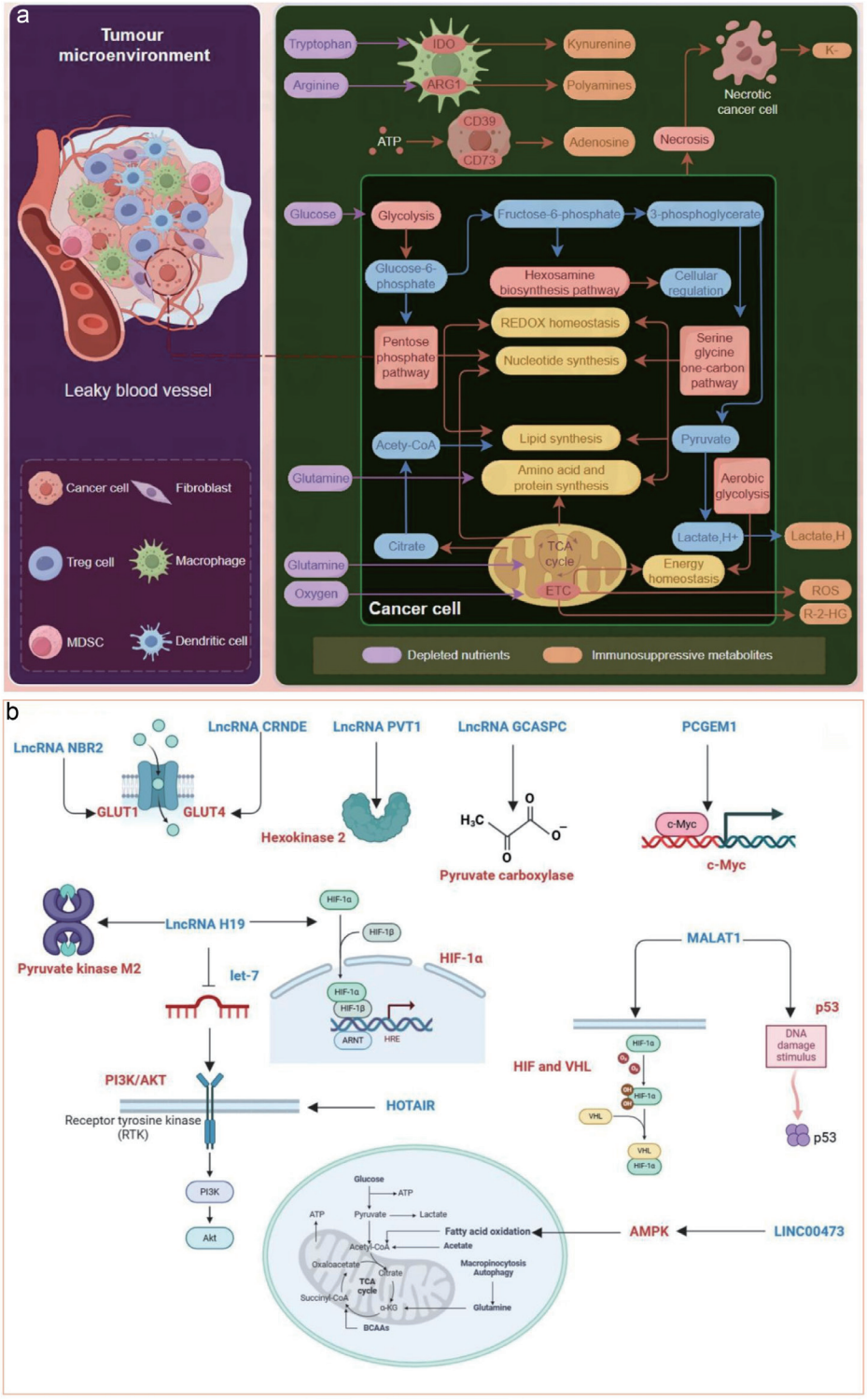

Fig. 4. Tumor microenvironment (TME) and tumor cell glucose metabolism regulated by some long non-coding RNAs (lncRNAs). (a) Schematic illustration of glucose metabolism in a tumor cell. (b) Role of lncRNAs in glucose metabolism in tumor cells. Key targets for lncRNAs may include glucose transporters 1/4 (GLUT-1/4) receptors, oncogenes (e.g., c-MYC), and enzymes (e.g., hexokinase 2). AKT, RAC-alpha serine/threonine-protein kinase; AMPK, AMP activated protein kinase; ARG1, arginase 1; ATP, molecule adenosine triphosphate; BCAAs, branched-chain amino acids; CD37, cluster of differentiation 37; CD39, cluster of differentiation 39; ETC, electron transport chain; HIF-1α, hypoxia-inducible factor 1-alpha; IDO, indoleamine 2,3-dioxygenase; PI3K, phosphoinositide 3-kinases; R-2-HG, oncometabolite (R)-2-hydroxyglutarate; ROS, reactive oxygen species; TCA cycle, tricarboxylic acid cycle; Treg, regulatory T cells; VHL, von Hippel-Lindau tumor suppressor.

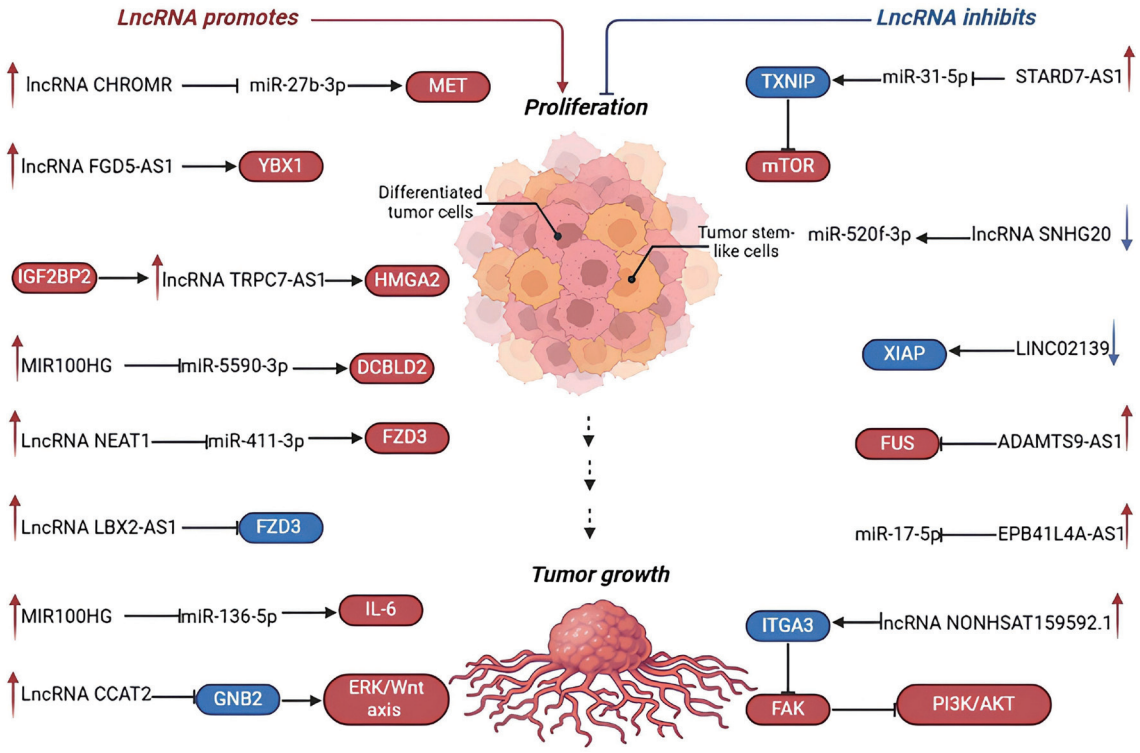

Fig. 5. The role of long non-coding RNAs (lncRNAs) in tumor cell proliferation and tumor growth. lncRNAs play a significant role in oncogenesis by regulating key processes in tumor cells, such as proliferative signaling. AKT, RAC-alpha serine/threonine-protein kinase; DCBLD2, discoidin, CUB and LCCL domain containing 2; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FUS, RNA-binding protein fused in sarcoma; FZD3, frizzled class receptor 3; GNB2, G protein subunit beta 2; HMGA2, high mobility group AT-Hook 2; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; IL-6, interleukin 6; ITGA3, integrin subunit alpha 3; MET, MET proto-oncogene; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinases; TXNIP, thioredoxin interacting protein; XIAP, X-linked inhibitor of apoptosis; YBX1, Y-Box binding protein 1.

tumor growth and metastasis. As research continues to uncover the diverse roles of lncRNAs in cancer, their use as therapeutic targets offers a promising direction for developing more effective cancer treatments. By integrating lncRNA-targeting strategies with existing therapies, it may be possible to enhance treatment outcomes and improve prognosis for patients with various forms of cancer.

Emerging technologies for lncRNA detection and therapeutic delivery

Advancements in molecular biology and nanotechnology have significantly improved strategies for detecting and delivering lncRNA-based therapies within the TME. These emerging technologies aim to improve the specificity, efficiency, and stability of both lncRNA detection and delivery mechanisms, ultimately improving therapeutic outcomes.

Next-generation sequencing has revolutionized the profiling of lncRNAs across various cancer types, enabling high-throughput identification of novel lncRNA biomarkers with increased resolution.[106] Recent improvements in single-cell next-generation sequencing techniques have refined the ability to detect lncRNA expression at the individual cell level, offering deeper insights into tumor heterogeneity and lncRNA functions in different cellular contexts.

CRISPR-Cas systems are increasingly tailored for the precise detection of specific lncRNAs in bodily fluids, offering unparalleled sensitivity and specificity. For example, CRISPR-Cas13-based diagnostic platforms can detect low-abundance lncRNAs in liquid biopsies, aiding early cancer detection and monitoring.[107] Additionally, innovations in CRISPR-Cas-mediated imaging techniques allow real-time visualization of lncRNA dynamics within live cells, providing valuable information on their spatial and temporal regulation.

Nanopore Sequencing technology has emerged as a powerful tool for real-time lncRNA sequencing, offering insights into their structural variations and post-transcriptional modifications. The development of high-throughput nanopore platforms has improved the resolution and accuracy of lncRNA sequencing, enabling the discovery of novel isoforms and their functional implications in cancer.[108] Recent enhancements in nanopore chemistry and signal processing have further improved the fidelity and speed of lncRNA detection, making it a viable option for clinical applications.

Nanoparticle-based delivery systems, including liposomes, dendrimers, and polymeric nanoparticles, have been engineered to deliver lncRNA-targeting molecules such as siRNAs and ASOs directly to tumor cells. These nanocarriers enhance the stability and cellular uptake of therapeutic agents while minimizing off-target effects. Advances in surface modification techniques have enabled the functionalization of nanoparticles with targeting ligands, increasing their specificity toward cancer cells and improving therapeutic efficacy.[109] For example, folate-conjugated liposomes have shown enhanced delivery of siRNA against oncogenic lncRNAs in ovarian cancer models.

Synthetic exosomes and exosome-mimicking vesicles represent another promising method for delivering lncRNA-based therapies.

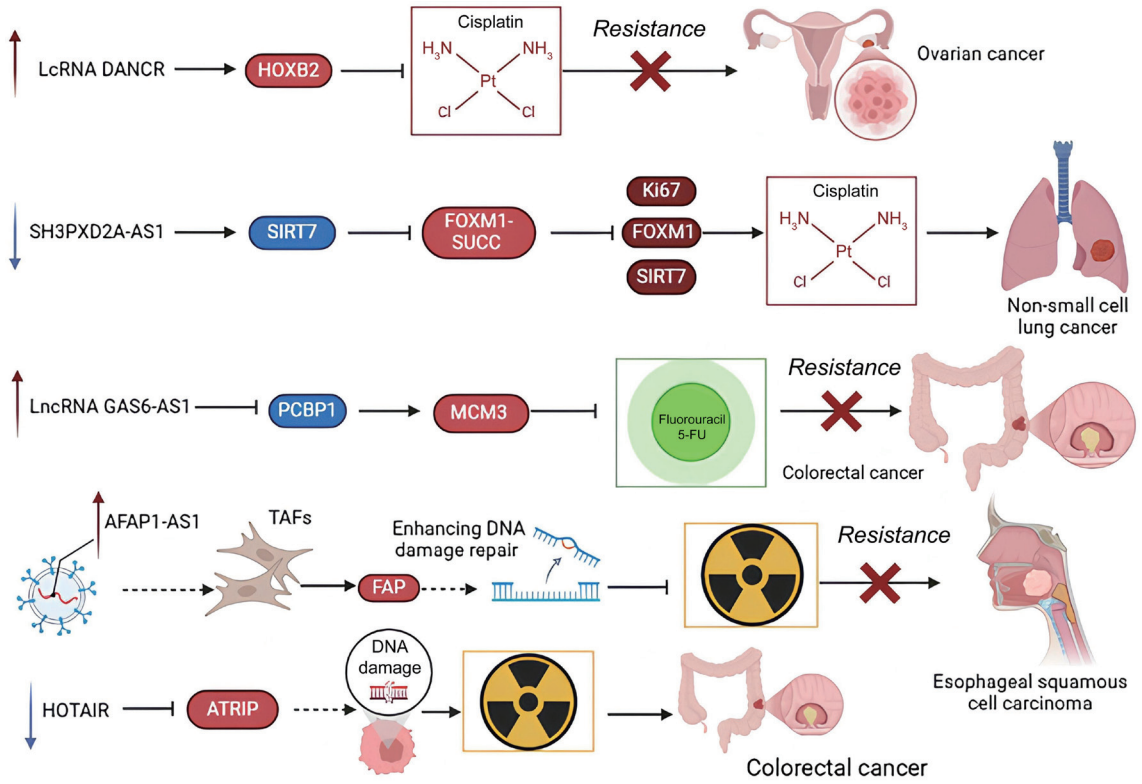

Fig. 6. Correlation between long non-coding RNAs (lncRNAs) and chemoradiotherapy resistance in tumors. lncRNAs have been reported to play a role in chemo- and radiotherapy resistance by impairing the response through cell cycle arrest, inhibition of apoptosis, and enhanced DNA damage repair. ATRIP, ATR interacting protein; FOXM1, forkhead box protein M1; HOXB2, homeobox B2; Ki67, marker of proliferation Kiel 67; MCM3, minichromosome maintenance complex component 3; PCBP1, poly(RC) binding protein 1; SIRT7, sirtuin 7; SUCC, succinate dehydrogenase complex subunit C; TAFs, tumor-associated fibroblasts.

Table 2. Potential clinical applications of long noncoding RNAs (lncRNAs)

Application area	Example lncRNA	Mechanism/Function	Clinical potential	Ref.
Biomarkers for diagnosis	PCA3	Overexpressed in prostate cancer.	FDA-approved biomarker for early prostate cancer detection.	94,95
	HOTAIR	Highly expressed in glioblastoma.	Non-invasive blood biomarker for glioblastoma diagnosis.	96
	TINCR, CCAT2, AOC4P, BANCR, and LINC00857	Panel improves gastric cancer diagnosis accuracy (AUC: 0.91).	Non-invasive diagnostic tool for gastric cancer.	97
	ZFAS1, SNHG11, LINC00909, and LINC00654	Biomarker panel improves colorectal cancer early detection.	Sensitive diagnostic tool for colorectal cancer.	98
Therapeutic targets	lncARSR	Promotes sunitinib resistance via miR-34/miR-449 competitive binding.	Enhances drug sensitivity in renal cell carcinoma.	103
	FLANC	Supports metastasis in colorectal cancer.	siRNA delivery via nanovesicles inhibits tumor progression.	104
	PKMYT1AR	Maintains cancer stem cells via β-catenin stabilization.	ASOs targeting to reduce tumor growth in non-small cell lung cancer.	105
	LINC00173.v1	Increases chemoresistance by promoting VEGFA expression in lung squamous cell carcinoma.	Antisense oligonucleotides inhibit tumor growth.	55
	CRNDE	Transferred via TAM-derived exosomes, degrades PTEN.	Targeting reverses cisplatin resistance in gastric cancer.	87

ASOs, antisense oligonucleotides; AUC, area under the ROC curve siRNA, small interfering RNA; FDA, U.S. Food and Drug Administration; PTEN, phosphatase and tensin homolog deleted on chromosome 10; TAMs, tumor-associated macrophages; VEGFA, vascular endothelial growth factor A.

These vesicles leverage the natural targeting capabilities and biocompatibility of exosomes to achieve high specificity in delivering therapeutic lncRNAs to tumor cells. Advances in exosome engineering, such as incorporating targeting peptides and optimizing loading techniques, have improved the efficiency and specificity of lncRNA delivery.[110] Recent studies have demonstrated the successful delivery of tumor-suppressive lncRNAs using engineered exosomes, resulting in significant tumor growth inhibition in preclinical models.

CRISPR/Cas9-based delivery systems are also being utilized to edit or modulate lncRNA expression within tumor cells, offering a precise method to alter lncRNA function. Innovations in CRISPR delivery, including the use of viral vectors, lipid nanoparticles, and cell-penetrating peptides (CPPs), have enhanced the efficiency and specificity of genome editing in cancer cells. Breakthroughs such as inducible CRISPR systems allow for temporal control over lncRNA editing, reducing potential off-target effects and improving therapeutic safety.[111] For example, lipid nanoparticle-encapsulated CRISPR/Cas9 has successfully targeted oncogenic lncRNAs in liver cancer models, demonstrating significant therapeutic potential.

Cell-penetrating peptides have been employed to facilitate the delivery of lncRNA-targeting molecules into cancer cells, enhancing therapeutic efficacy. CPPs such as TAT and penetratin have been conjugated with siRNAs and ASOs to improve cellular uptake and stability. Recent advancements in CPP design, including the incorporation of stimuli-responsive elements, have allowed for controlled release of therapeutic agents in the TME, further increasing the precision of lncRNA-based therapies.[112] Recent studies have shown that CPP-mediated delivery of lncRNA inhibitors can effectively suppress tumor growth and metastasis in various cancer models.

The integration of cutting-edge molecular biology techniques and nanotechnology has significantly advanced the detection and therapeutic delivery of lncRNAs in cancer. These emerging technologies not only improve the precision and efficiency of lncRNA-based interventions but also pave the way for personalized, targeted cancer therapies. Ongoing research and development in this field hold great promise for improving cancer diagnosis, prognosis, and treatment outcomes.

Limitations of this review

While this review provides a comprehensive overview of the roles of lncRNAs in the TME, several limitations must be acknowledged. The review primarily focuses on studies published up to 2023, meaning that recent advancements beyond this period may not be fully captured. Although multiple cancer types are discussed, the vast heterogeneity among cancers means that some specific interactions between lncRNAs and the TME may not be thoroughly covered. While significant mechanisms are highlighted, the complex and multifaceted roles of lncRNAs in cancer biology still require further elucidation through more detailed mechanistic studies. The translation of preclinical findings into clinical applications is still in its early stages, and this review may not fully address the challenges or progress in clinical trials involving lncRNA-targeted therapies. Additionally, emerging technologies for lncRNA detection and delivery are rapidly evolving, and the review may not encompass the latest innovations or their potential applications. Addressing these limitations in future research will provide a more nuanced and detailed understanding of the intricate roles of lncRNAs in cancer and their potential as therapeutic targets.

Conclusions and future directions

Aberrantly expressed lncRNAs within the TME are emerging as critical players in tumor growth, progression, metastasis, and drug resistance. These lncRNAs influence a wide range of cellular processes, including the regulation of gene expression, modulation of cell signaling pathways, and interactions with various components of the immune system and ECM. Their role in shaping the complex interactions between cancer cells and their microenvironment makes them vital for sustaining tumor development. Additionally, lncRNAs regulate processes such as EMT, angiogenesis, immune evasion, and the maintenance of cancer stem cells, all of which contribute to tumor aggressiveness and therapy resistance. As research continues to explore the roles and mechanisms of lncRNAs in the TME, it holds great potential for uncovering new insights into tumor pathogenesis and progression. This expanding knowledge could pave the way for developing novel therapeutic strategies specifically targeting lncRNAs, offering more precise and effective cancer treatments. For example, targeting lncRNAs involved in immune evasion could enhance immunotherapy efficacy, while inhibiting lncRNAs that promote metastasis may help prevent cancer spread. Despite these promising prospects, the clinical application of lncRNAs as therapeutic targets remains in its early stages, with several significant challenges still to overcome. One major hurdle is the complexity and diversity of lncRNAs' functions, which require a thorough understanding of the context-specific mechanisms through which they operate. Furthermore, developing robust and specific strategies for lncRNA knockdown or inhibition is essential to avoid off-target effects that could lead to unintended consequences. Identifying suitable delivery systems for targeting lncRNAs within the TME is also critical, as these molecules are often difficult to deliver effectively due to their size and structure.

Future research should focus on overcoming these challenges by elucidating the diverse mechanisms through which lncRNAs exert their effects, optimizing methods for specific and efficient lncRNA inhibition, and designing innovative delivery systems that can target lncRNAs within the TME with high precision. Addressing these challenges will be crucial for translating the potential of lncRNAs into tangible clinical benefits, ultimately improving outcomes for cancer patients. With continued progress, lncRNAs could become valuable therapeutic targets, revolutionizing cancer treatment and offering new hope for patients facing advanced and drug-resistant cancers.

Acknowledgments

The authors have utilized the highly esteemed software, Biorender, to create the figures for this manuscript. BioRender.com (2025). Retrieved from https://www.biorender.com/.

Funding

This work was supported by the Bashkir State Medical University Strategic Academic Leadership Program (PRIORITY-2030).

Conflict of interest

Ilgiz Gareev has been an editorial board member of *Gene Expression* since February 2025. Irina Popova is an employee of the medical center at PJSC Novatek and the medical center of LLC "Sherwood Premier" in Moscow, Russia.

Author contributions

Study conception, study design (OB), data acquisition, analysis, and interpretation (EM, CW), drafting of the manuscript (OB), critical revisions of the manuscript (IG), writing – review & editing (IP), and supervision (OB). All authors agreed on the journal to which the article would be submitted, gave the final approval to the version to be published, and agreed to take responsibility for all aspects of the work.

References

[1] Tufail M, Jiang CH, Li N. Altered metabolism in cancer: insights into energy pathways and therapeutic targets. Mol Cancer 2024;23(1):203. doi:10.1186/s12943-024-02119-3, PMID:39294640.

[2] Flamini V, Jiang WG, Lane J, Cui YX. Significance and therapeutic implications of endothelial progenitor cells in angiogenic-mediated tumour metastasis. Crit Rev Oncol Hematol 2016;100:177–189. doi:10.1016/j.critrevonc.2016.02.010, PMID:26917455.

[3] Poyia F, Neophytou CM, Christodoulou MI, Papageorgis P. The Role of Tumor Microenvironment in Pancreatic Cancer Immunotherapy: Current Status and Future Perspectives. Int J Mol Sci 2024;25(17):9555. doi:10.3390/ijms25179555, PMID:39273502.

[4] Beylerli O, Gareev I, Sufianov A, Ilyasova T, Guang Y. Long noncoding RNAs as promising biomarkers in cancer. Noncoding RNA Res 2022;7(2):66–70. doi:10.1016/j.ncrna.2022.02.004, PMID:35310927.

[5] Beylerli O, Gareev I, Pavlov V, Chen X, Zhao S. The Role of Long Noncoding RNAs in the Biology of Pituitary Adenomas. World Neurosurg 2020;137:252–256. doi:10.1016/j.wneu.2019.10.137, PMID:31678448.

[6] Gareev I, Kudriashov V, Sufianov A, Begliarzade S, Ilyasova T, Liang Y, *et al*. The role of long non-coding RNA ANRIL in the development of atherosclerosis. Noncoding RNA Res 2022;7(4):212–216. doi:10.1016/j.ncrna.2022.09.002, PMID:36157350.

[7] Deniz E, Erman B. Long noncoding RNA (lincRNA), a new paradigm in gene expression control. Funct Integr Genomics 2017;17(2-3):135–143. doi:10.1007/s10142-016-0524-x, PMID:27681237.

[8] Zhang F, Zhang L, Zhang C. Long noncoding RNAs and tumorigenesis: genetic associations, molecular mechanisms, and therapeutic strategies. Tumour Biol 2016;37(1):163–175. doi:10.1007/s13277-015-4445-4, PMID:26586396.

[9] Billerey C, Boussaha M, Esquerré D, Rebours E, Djari A, Meersseman C, *et al*. Identification of large intergenic non-coding RNAs in bovine muscle using next-generation transcriptomic sequencing. BMC Genomics 2014;15(1):499. doi:10.1186/1471-2164-15-499, PMID:24948191.

[10] Gareev I, Beylerli O, Aliev G, Pavlov V, Izmailov A, Zhang Y, *et al*. The Role of Long Non-Coding RNAs in Intracranial Aneurysms and Subarachnoid Hemorrhage. Life (Basel) 2020;10(9):155. doi:10.3390/life10090155, PMID:32825276.

[11] Tan JY, Biasini A, Young RS, Marques AC. Splicing of enhancer-associated lincRNAs contributes to enhancer activity. Life Sci Alliance 2020;3(4):e202000663. doi:10.26508/lsa.202000663, PMID:32086317.

[12] Strehle M, Guttman M. Xist drives spatial compartmentalization of DNA and protein to orchestrate initiation and maintenance of X inactivation. Curr Opin Cell Biol 2020;64:139–147. doi:10.1016/j.ceb.2020.04.009, PMID:32535328.

[13] Soghli N, Yousefi T, Abolghasemi M, Qujeq D. NORAD, a critical long non-coding RNA in human cancers. Life Sci 2021;264:118665. doi:10.1016/j.lfs.2020.118665, PMID:33127516.

[14] Begliarzade S, Beilerli A, Sufianov A, Tamrazov R, Kudriashov V, Ilyasova T, *et al*. Long non-coding RNAs as promising biomarkers and therapeutic targets in cervical cancer. Noncoding RNA Res 2023;8(2):233–239. doi:10.1016/j.ncrna.2023.02.006, PMID:36890809.

[15] Singh RN, Singh NN. A novel role of U1 snRNP: Splice site selection from a distance. Biochim Biophys Acta Gene Regul Mech 2019;1862(6):634–642. doi:10.1016/j.bbagrm.2019.04.004, PMID:31042550.

[16] Beylerli O, Ju J, Beilerli A, Gareev I, Shumadalova A, Ilyasova T, *et al*. The roles of long noncoding RNAs in atrial fibrillation. Noncoding RNA Res 2023;8(4):542–549. doi:10.1016/j.ncrna.2023.08.004, PMID:37602317.

[17] Meier K, Brehm A. Chromatin regulation: how complex does it get? Epigenetics 2014;9(11):1485–1495. doi:10.4161/15592294.2014.971580, PMID:25482055.

[18] Trotman JB, Braceros KCA, Cherney RE, Murvin MM, Calabrese JM. The control of polycomb repressive complexes by long noncoding RNAs. Wiley Interdiscip Rev RNA 2021;12(6):e1657. doi:10.1002/wrna.1657, PMID:33861025.

[19] Zhang Y, Liu H, Niu M, Wang Y, Xu R, Guo Y, *et al*. Roles of long noncoding RNAs in human inflammatory diseases. Cell Death Discov 2024;10(1):235. doi:10.1038/s41420-024-02002-6, PMID:38750059.

[20] Nickerson JA, Momen-Heravi F. Long non-coding RNAs: roles in cellular stress responses and epigenetic mechanisms regulating chromatin. Nucleus 2024;15(1):2350180. doi:10.1080/19491034.2024.2350180, PMID:38773934.

[21] Noh JH, Kim KM, Abdelmohsen K, Yoon JH, Panda AC, Munk R, *et al*. HuR and GRSF1 modulate the nuclear export and mitochondrial localization of the lncRNA RMRP. Genes Dev 2016;30(10):1224–1239. doi:10.1101/gad.276022.115, PMID:27198227.

[22] Kadian LK, Verma D, Lohani N, Yadav R, Ranga S, Gulshan G, *et al*. Long non-coding RNAs in cancer: multifaceted roles and potential targets for immunotherapy. Mol Cell Biochem 2024;479(12):3229–3254. doi:10.1007/s11010-024-04933-1, PMID:38413478.

[23] Guo K, Qian K, Shi Y, Sun T, Wang Z. LncRNA-MIAT promotes thyroid cancer progression and function as ceRNA to target EZH2 by sponging miR-150-5p. Cell Death Dis 2021;12(12):1097. doi:10.1038/s41419-021-04386-0, PMID:34811354.

[24] Qi X, Zhang DH, Wu N, Xiao JH, Wang X, Ma W. ceRNA in cancer: possible functions and clinical implications. J Med Genet 2015;52(10):710–718. doi:10.1136/jmedgenet-2015-103334, PMID:26358722.

[25] Hou P, Meng S, Li M, Lin T, Chu S, Li Z, *et al*. LINC00460/DHX9/IGF2BP2 complex promotes colorectal cancer proliferation and metastasis by mediating HMGA1 mRNA stability depending on m6A modification. J Exp Clin Cancer Res 2021;40(1):52. doi:10.1186/s13046-021-01857-2, PMID:33526059.

[26] Bach DH, Lee SK. Long noncoding RNAs in cancer cells. Cancer Lett 2018;419:152–166. doi:10.1016/j.canlet.2018.01.053, PMID:29414303.

[27] Slack FJ, Chinnaiyan AM. The Role of Non-coding RNAs in Oncology. Cell 2019;179(5):1033–1055. doi:10.1016/j.cell.2019.10.017, PMID:31730848.

[28] Liu SJ, Dang HX, Lim DA, Feng FY, Maher CA. Long noncoding RNAs in cancer metastasis. Nat Rev Cancer 2021;21(7):446–460. doi:10.1038/s41568-021-00353-1, PMID:33953369.

[29] Lu X, Wang J, Wang W, Lu C, Qu T, He X, *et al*. Copy number amplification and SP1-activated lncRNA MELTF-AS1 regulates tumorigenesis by driving phase separation of YBX1 to activate ANXA8 in non-small cell lung cancer. Oncogene 2022;41(23):3222–3238. doi:10.1038/s41388-022-02292-z, PMID:35508543.

[30] Song H, Adu-Amankwaah J, Zhao Q, Yang D, Liu K, Bushi A, *et al*. Decoding long non-coding RNAs: Friends and foes in cancer development (Review). Int J Oncol 2024;64(6):61. doi:10.3892/ijo.2024.5649, PMID:38695241.

[31] Jin W, Jia J, Si Y, Liu J, Li H, Zhu H, *et al*. Identification of Key lncRNAs Associated with Immune Infiltration and Prognosis in Gastric Cancer. Biochem Genet 2024. doi:10.1007/s10528-024-10801-w.

[32] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144(5):646–674. doi:10.1016/j.cell.2011.02.013, PMID:21376230.

[33] Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. Cancer Discov 2011;1(5):391–407. doi:10.1158/2159-8290.CD-11-0209, PMID:22096659.

[34] Endo H, Shiroki T, Nakagawa T, Yokoyama M, Tamai K, Yamanami H, *et al*. Enhanced expression of long non-coding RNA HOTAIR is associated with the development of gastric cancer. PLoS One 2013;8(10):e77070. doi:10.1371/journal.pone.0077070, PMID:24130837.

[35] Huarte M. The emerging role of lncRNAs in cancer. Nat Med 2015;21(11):1253–1261. doi:10.1038/nm.3981, PMID:26540387.

[36] Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, *et al*. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 2010;464(7291):1071–1076. doi:10.1038/nature08975, PMID:20393566.

[37] Hung T, Chang HY. Long noncoding RNA in genome regulation: prospects and mechanisms. RNA Biol 2010;7(5):582–585. doi:10.4161/rna.7.5.13216, PMID:20930520.
[38] Zhang XN, Zhou J, Lu XJ. The long noncoding RNA NEAT1 contributes to hepatocellular carcinoma development by sponging miR-485 and enhancing the expression of the STAT3. J Cell Physiol 2018;233(9):6733–6741. doi:10.1002/jcp.26371, PMID:29219178.
[39] Zhang Y, Liu Q, Liao Q. Long noncoding RNA: a dazzling dancer in tumor immune microenvironment. J Exp Clin Cancer Res 2020;39(1):231. doi:10.1186/s13046-020-01727-3, PMID:33148302.
[40] Su P, Mu S, Wang Z. Long Noncoding RNA SNHG16 Promotes Osteosarcoma Cells Migration and Invasion via Sponging miRNA-340. DNA Cell Biol 2019;38(2):170–175. doi:10.1089/dna.2018.4424, PMID:30726150.
[41] Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, *et al*. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell 2010;39(6):925–938. doi:10.1016/j.molcel.2010.08.011, PMID:20797886.
[42] Lu YF, Cai XL, Li ZZ, Lv J, Xiang YA, Chen JJ, *et al*. LncRNA SNHG16 Functions as an Oncogene by Sponging MiR-4518 and Up-Regulating PRMT5 Expression in Glioma. Cell Physiol Biochem 2018;45(5):1975–1985. doi:10.1159/000487974, PMID:29529599.
[43] Jiang R, Tang J, Chen Y, Deng L, Ji J, Xie Y, *et al*. The long noncoding RNA lnc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion. Nat Commun 2017;8:15129. doi:10.1038/ncomms15129, PMID:28541302.
[44] Yu L, Chen D, Song J. LncRNA SNHG16 promotes non-small cell lung cancer development through regulating EphA2 expression by sponging miR-520a-3p. Thorac Cancer 2020;11(3):603–611. doi:10.1111/1759-7714.13304, PMID:31953899.
[45] Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, *et al*. Oral squamous cell carcinomas: state of the field and emerging directions. Int J Oral Sci 2023;15(1):44. doi:10.1038/s41368-023-00249-w, PMID:37736748.
[46] Mao TL, Fan MH, Dlamini N, Liu CL. LncRNA MALAT1 Facilitates Ovarian Cancer Progression through Promoting Chemoresistance and Invasiveness in the Tumor Microenvironment. Int J Mol Sci 2021;22(19):10201. doi:10.3390/ijms221910201, PMID:34638541.
[47] Zhang H, Hua Y, Jiang Z, Yue J, Shi M, Zhen X, *et al*. Cancer-associated Fibroblast-promoted LncRNA DNM3OS Confers Radioresistance by Regulating DNA Damage Response in Esophageal Squamous Cell Carcinoma. Clin Cancer Res 2019;25(6):1989–2000. doi:10.1158/1078-0432.CCR-18-0773, PMID:30463848.
[48] Li W, Zhang H, You Z, Guo B. LncRNAs in Immune and Stromal Cells Remodel Phenotype of Cancer Cell and Tumor Microenvironment. J Inflamm Res 2024;17:3173–3185. doi:10.2147/JIR.S460730, PMID:38774447.
[49] Yin J, Zhu W, Feng S, Yan P, Qin S. The role of cancer-associated fibroblasts in the invasion and metastasis of colorectal cancer. Front Cell Dev Biol 2024;12:1375543. doi:10.3389/fcell.2024.1375543, PMID:39139454.
[50] Güzel Tanoğlu E, Adigüzel S, Tanoğlu A, Aydin ZB, Hocaoğlu G, Ebinç S. Long noncoding RNAs in pancreas cancer: from biomarkers to therapeutic targets. Turk J Med Sci 2023;53(6):1552–1564. doi:10.55730/1300-0144.5724, PMID:38813489.
[51] Zhou X, Yan Y, Shen Y, Xu M, Xu W. Exosomes: Emerging Insights into the Progression of Pancreatic Cancer. Int J Biol Sci 2024;20(10):4098–4113. doi:10.7150/ijbs.97076, PMID:39113699.
[52] Conigliaro A, Costa V, Lo Dico A, Saieva L, Buccheri S, Dieli F, *et al*. CD90+ liver cancer cells modulate endothelial cell phenotype through the release of exosomes containing H19 lncRNA. Mol Cancer 2015;14:155. doi:10.1186/s12943-015-0426-x, PMID:26272696.
[53] Hu J, Peng F, Qiu X, Yang J, Li J, Shen C, *et al*. NR2F1-AS1: A Functional Long Noncoding RNA in Tumorigenesis. Curr Med Chem 2023;30(37):4266–4276. doi:10.2174/0929867330666230112165503, PMID:36644870.
[54] Zhou DD, Liu XF, Lu CW, Pant OP, Liu XD. Long non-coding RNA PVT1: Emerging biomarker in digestive system cancer. Cell Prolif 2017;50(6):e12398. doi:10.1111/cpr.12398, PMID:29027279.
[55] Chen J, Liu A, Wang Z, Wang B, Chai X, Lu W, *et al*. LINC00173.v1 promotes angiogenesis and progression of lung squamous cell carcinoma by sponging miR-511-5p to regulate VEGFA expression. Mol Cancer 2020;19(1):98. doi:10.1186/s12943-020-01217-2, PMID:32473645.
[56] Chen D, Zhang X, Li Z, Zhu B. Metabolic regulatory crosstalk between tumor microenvironment and tumor-associated macrophages. Theranostics 2021;11(3):1016–1030. doi:10.7150/thno.51777, PMID:33391518.
[57] Liu J, Liu ZX, Li JJ, Zeng ZL, Wang JH, Luo XJ, *et al*. The Macrophage-Associated LncRNA MALR Facilitates ILF3 Liquid-Liquid Phase Separation to Promote HIF1α Signaling in Esophageal Cancer. Cancer Res 2023;83(9):1476–1489. doi:10.1158/0008-5472.CAN-22-1922, PMID:36264156.
[58] Chen F, Chen J, Yang L, Liu J, Zhang X, Zhang Y, *et al*. Extracellular vesicle-packaged HIF-1α-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat Cell Biol 2019;21(4):498–510. doi:10.1038/s41556-019-0299-0, PMID:30936474.
[59] Rahmati S, Moeinafshar A, Rezaei N. The multifaceted role of extracellular vesicles (EVs) in colorectal cancer: metastasis, immune suppression, therapy resistance, and autophagy crosstalk. J Transl Med 2024;22(1):452. doi:10.1186/s12967-024-05267-8, PMID:38741166.
[60] Sun C, Li S, Zhang F, Xi Y, Wang L, Bi Y, *et al*. Long non-coding RNA NEAT1 promotes non-small cell lung cancer progression through regulation of miR-377-3p-E2F3 pathway. Oncotarget 2016;7(32):51784–51814. doi:10.18632/oncotarget.10108, PMID:27351135.
[61] Feichtenschlager V, Zheng YJ, Ho W, Chen L, Callanan C, Chen C, *et al*. Deconstructing the role of MALAT1 in MAPK-signaling in melanoma: insights from antisense oligonucleotide treatment. Oncotarget 2023;14:543–560. doi:10.18632/oncotarget.28447, PMID:37235843.
[62] Shao H, Dong D, Shao F. Long non-coding RNA TUG1-mediated down-regulation of KLF4 contributes to metastasis and the epithelial-to-mesenchymal transition of colorectal cancer by miR-153-1. Cancer Manag Res 2019;11:8699–8710. doi:10.2147/CMAR.S208508, PMID:31576172.
[63] Ma J, Zheng B, Goswami S, Meng L, Zhang D, Cao C, *et al*. PD1(Hi) CD8(+) T cells correlate with exhausted signature and poor clinical outcome in hepatocellular carcinoma. J Immunother Cancer 2019;7(1):331. doi:10.1186/s40425-019-0814-7, PMID:31783783.
[64] Showalter LE, Oechsle C, Ghimirey N, Steele C, Czerniecki BJ, Koski GK. Th1 cytokines sensitize HER-expressing breast cancer cells to lapatinib. PLoS One 2019;14(1):e0210209. doi:10.1371/journal.pone.0210209, PMID:30657766.
[65] Tecalco-Cruz AC, Medina-Abreu KH, Oropeza-Martínez E, Zepeda-Cervantes J, Vázquez-Macías A, Macías-Silva M. Deregulation of interferon-gamma receptor 1 expression and its implications for lung adenocarcinoma progression. World J Clin Oncol 2024;15(2):195–207. doi:10.5306/wjco.v15.i2.195, PMID:38455133.
[66] Wambecke A, Ahmad M, Morice PM, Lambert B, Weiswald LB, Vernon M, *et al*. The lncRNA 'UCA1' modulates the response to chemotherapy of ovarian cancer through direct binding to miR-27a-5p and control of UBE2N levels. Mol Oncol 2021;15(12):3659–3678. doi:10.1002/1878-0261.13045, PMID:34160887.
[67] Dong S, Zhang X, Liu D. Overexpression of long noncoding RNA GAS5 suppresses tumorigenesis and development of gastric cancer by sponging miR-106a-5p through the Akt/mTOR pathway. Biol Open 2019;8(6):bio041343. doi:10.1242/bio.041343, PMID:31182630.
[68] Sun J, Xin K, Leng C, Ge J. Down-regulation of SNHG16 alleviates the acute lung injury in sepsis rats through miR-128-3p/HMGB3 axis. BMC Pulm Med 2021;21(1):191. doi:10.1186/s12890-021-01552-0, PMID:34092219.
[69] Wang F, Lau JKC, Yu J. The role of natural killer cell in gastrointestinal cancer: killer or helper. Oncogene 2021;40(4):717–730. doi:10.1038/s41388-020-01561-z, PMID:33262461.
[70] Pesce S, Greppi M, Ferretti E, Obino V, Carlomagno S, Rutigliani M, *et al*. miRNAs in NK Cell-Based Immune Responses and Cancer Immunotherapy. Front Cell Dev Biol 2020;8:119. doi:10.3389/fcell.2020.00119, PMID:32161759.
[71] Fang P, Xiang L, Chen W, Li S, Huang S, Li J, *et al*. LncRNA GAS5 enhanced the killing effect of NK cell on liver cancer through regulating miR-544/RUNX3. Innate Immun 2019;25(2):99–109. doi:10.1177/1753425919827632, PMID:30774011.
[72] Liu C, Tian X, Zhang J, Jiang L. Long Non-coding RNA DLEU1 Promotes

Proliferation and Invasion by Interacting With miR-381 and Enhancing HOXA13 Expression in Cervical Cancer. Front Genet 2018;9:629. doi:10.3389/fgene.2018.00629, PMID:30581456.
[73] Wang J, Wang Q, Guan Y, Sun Y, Wang X, Lively K, *et al*. Breast cancer cell-derived microRNA-155 suppresses tumor progression via enhancing immune cell recruitment and antitumor function. J Clin Invest 2022;132(19):e157248. doi:10.1172/JCI157248, PMID:35925680.
[74] Della Chiesa M, Setti C, Giordano C, Obino V, Greppi M, Pesce S, *et al*. NK Cell-Based Immunotherapy in Colorectal Cancer. Vaccines (Basel) 2022;10(7):1033. doi:10.3390/vaccines10071033, PMID:35891197.
[75] Cantile M, Di Bonito M, Tracey De Bellis M, Botti G. Functional Interaction among lncRNA HOTAIR and MicroRNAs in Cancer and Other Human Diseases. Cancers (Basel) 2021;13(3):570. doi:10.3390/cancers13030570, PMID:33540611.
[76] Chen Y, Yi X, Sun N, Guo W, Li C. Epigenetics Regulates Antitumor Immunity in Melanoma. Front Immunol 2022;13:868786. doi:10.3389/fimmu.2022.868786, PMID:35693795.
[77] Tang L, Chen Y, Tang X, Wei D, Xu X, Yan F. Long Noncoding RNA DCST1-AS1 Promotes Cell Proliferation and Metastasis in Triple-negative Breast Cancer by Forming a Positive Regulatory Loop with miR-873-5p and MYC. J Cancer 2020;11(2):311–323. doi:10.7150/jca.33982, PMID:31897227.
[78] Zhang J, Thakuri BKC, Zhao J, Nguyen LN, Nguyen LNT, Khanal S, *et al*. Long Noncoding RNA RUNXOR Promotes Myeloid-Derived Suppressor Cell Expansion and Functions via Enhancing Immunosuppressive Molecule Expressions during Latent HIV Infection. J Immunol 2021;206(9):2052–2060. doi:10.4049/jimmunol.2001008, PMID:33820854.
[79] Fonseca TS, Martins RM, Rolo AP, Palmeira CM. SNHG1: Redefining the Landscape of Hepatocellular Carcinoma through Long Noncoding RNAs. Biomedicines 2024;12(8):1696. doi:10.3390/biomedicines12081696, PMID:39200161.
[80] de Oliveira JC, Oliveira LC, Mathias C, Pedroso GA, Lemos DS, Salviano-Silva A, *et al*. Long non-coding RNAs in cancer: Another layer of complexity. J Gene Med 2019;21(1):e3065. doi:10.1002/jgm.3065, PMID:30549380.
[81] Peng PH, Hsu KW, Chieh-Yu Lai J, Wu KJ. The role of hypoxia-induced long noncoding RNAs (lncRNAs) in tumorigenesis and metastasis. Biomed J 2021;44(5):521–533. doi:10.1016/j.bj.2021.03.005, PMID:34654684.
[82] Yang P, Yang W, Wei Z, Li Y, Yang Y, Wang J. Novel targets for gastric cancer: The tumor microenvironment (TME), N6-methyladenosine (m6A), pyroptosis, autophagy, ferroptosis and cuproptosis. Biomed Pharmacother 2023;163:114883. doi:10.1016/j.biopha.2023.114883, PMID:37196545.
[83] Mou J, Li C, Zheng Q, Meng X, Tang H. Research progress in tumor angiogenesis and drug resistance in breast cancer. Cancer Biol Med 2024;21(7):571–585. doi:10.20892/j.issn.2095-3941.2023.0515, PMID:38940663.
[84] Beylerli O, Tamrazov R, Gareev I, Ilyasova T, Shumadalova A, Bai Y, *et al*. Role of exosomal ncRNAs in traumatic brain injury. Noncoding RNA Res 2023;8(4):686–692. doi:10.1016/j.ncrna.2023.10.004, PMID:37860267.
[85] Sun J, Sun Z, Gareev I, Yan T, Chen X, Ahmad A, *et al*. Exosomal miR-2276-5p in Plasma Is a Potential Diagnostic and Prognostic Biomarker in Glioma. Front Cell Dev Biol 2021;9:671202. doi:10.3389/fcell.2021.671202, PMID:34141710.
[86] Sufianov A, Kostin A, Begliarzade S, Kudriashov V, Ilyasova T, Liang Y, *et al*. Exosomal non coding RNAs as a novel target for diabetes mellitus and its complications. Noncoding RNA Res 2023;8(2):192–204. doi:10.1016/j.ncrna.2023.02.001, PMID:36818396.
[87] Xin L, Zhou LQ, Liu C, Zeng F, Yuan YW, Zhou Q, *et al*. Transfer of LncRNA CRNDE in TAM-derived exosomes is linked with cisplatin resistance in gastric cancer. EMBO Rep 2021;22(12):e52124. doi:10.15252/embr.202052124, PMID:34647680.
[88] Wei T, Song J, Liang K, Li L, Mo X, Huang Z, *et al*. Identification of a novel therapeutic candidate, NRK, in primary cancer-associated fibroblasts of lung adenocarcinoma microenvironment. J Cancer Res Clin Oncol 2021;147(4):1049–1064. doi:10.1007/s00432-020-03489-z, PMID:33387038.
[89] Ahmad S, Abbas M, Ullah MF, Aziz MH, Beylerli O, Alam MA, *et al*. Long non-coding RNAs regulated NF-κB signaling in cancer metastasis: Micromanaging by not so small non-coding RNAs. Semin Cancer Biol 2022;85:155–163. doi:10.1016/j.semcancer.2021.07.015, PMID:34314819.
[90] Xie Y, Zhang Y, Du L, Jiang X, Yan S, Duan W, *et al*. Circulating long noncoding RNA act as potential novel biomarkers for diagnosis and prognosis of non-small cell lung cancer. Mol Oncol 2018;12(5):648–658. doi:10.1002/1878-0261.12188, PMID:29504701.
[91] Zhang M, Yu X, Zhang Q, Sun Z, He Y, Guo W. MIR4435-2HG: A newly proposed lncRNA in human cancer. Biomed Pharmacother 2022;150:112971. doi:10.1016/j.biopha.2022.112971, PMID:35447550.
[92] Yang Q, Tian H, Guo Z, Ma Z, Wang G. The role of noncoding RNAs in the tumor microenvironment of hepatocellular carcinoma. Acta Biochim Biophys Sin (Shanghai) 2023;55(11):1697–1706. doi:10.3724/abbs.2023231, PMID:37867435.
[93] Ouyang Q, Zhou J, Yang W, Cui H, Xu M, Yi L. Oncogenic role of neurotensin and neurotensin receptors in various cancers. Clin Exp Pharmacol Physiol 2017;44(8):841–846. doi:10.1111/1440-1681.12787, PMID:28556374.
[94] Shen H, Jin Y, Zhao H, Wu M, Zhang K, Wei Z, *et al*. Potential clinical utility of liquid biopsy in early-stage non-small cell lung cancer. BMC Med 2022;20(1):480. doi:10.1186/s12916-022-02681-x, PMID:36514063.
[95] Zhang S, Xia Y, Chen W, Dong H, Cui B, Liu C, *et al*. Regulation and Therapeutic Application of Long non-Coding RNA in Tumor Angiogenesis. Technol Cancer Res Treat 2024;23:15330338241273239. doi:10.1177/15330338241273239, PMID:39110070.
[96] Lu E, Gareev I, Yuan C, Liang Y, Sun J, Chen X, *et al*. The Mechanisms of Current Platinum Anticancer Drug Resistance in the Glioma. Curr Pharm Des 2022;28(23):1863–1869. doi:10.2174/1381612828666220607105746, PMID:35674307.
[97] Gareev I, Ahmad A, Wang J, Beilerli A, Ilyasova T, Sufianov A, *et al*. Gastric juice non-coding RNAs as potential biomarkers for gastric cancer. Front Physiol 2023;14:1179582. doi:10.3389/fphys.2023.1179582, PMID:37179825.
[98] Xu W, Zhou G, Wang H, Liu Y, Chen B, Chen W, *et al*. Circulating lncRNA SNHG11 as a novel biomarker for early diagnosis and prognosis of colorectal cancer. Int J Cancer 2020;146(10):2901–2912. doi:10.1002/ijc.32747, PMID:31633800.
[99] Chen Z, Han F, Du Y, Shi H, Zhou W. Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther 2023;8(1):70. doi:10.1038/s41392-023-01332-8, PMID:36797231.
[100] Cheng W, Mi W, Wang S, Wang X, Jiang H, Chen J, *et al*. Dissection of triple-negative breast cancer microenvironment and identification of potential therapeutic drugs using single-cell RNA sequencing analysis. J Pharm Anal 2024;14(8):100975. doi:10.1016/j.jpha.2024.100975, PMID:39263352.
[101] Toden S, Zumwalt TJ, Goel A. Non-coding RNAs and potential therapeutic targeting in cancer. Biochim Biophys Acta Rev Cancer 2021;1875(1):188491. doi:10.1016/j.bbcan.2020.188491, PMID:33316377.
[102] Nemeth K, Bayraktar R, Ferracin M, Calin GA. Non-coding RNAs in disease: from mechanisms to therapeutics. Nat Rev Genet 2024;25(3):211–232. doi:10.1038/s41576-023-00662-1, PMID:37968332.
[103] Huang K, Yu L, Lu D, Zhu Z, Shu M, Ma Z. Long non-coding RNAs in ferroptosis, pyroptosis and necroptosis: from functions to clinical implications in cancer therapy. Front Oncol 2024;14:1437698. doi:10.3389/fonc.2024.1437698, PMID:39267831.
[104] Oh CK, Cho YS. Pathogenesis and biomarkers of colorectal cancer by epigenetic alteration. Intest Res 2024;22(2):131–151. doi:10.5217/ir.2023.00115, PMID:38295766.
[105] He Y, Jiang X, Duan L, Xiong Q, Yuan Y, Liu P, *et al*. LncRNA PKMYT1AR promotes cancer stem cell maintenance in non-small cell lung cancer via activating Wnt signaling pathway. Mol Cancer 2021;20(1):156. doi:10.1186/s12943-021-01469-6, PMID:34856993.
[106] Zeng D, Ye Z, Shen R, Yu G, Wu J, Xiong Y, *et al*. IOBR: Multi-Omics Immuno-Oncology Biological Research to Decode Tumor Microenvironment and Signatures. Front Immunol 2021;12:687975. doi:10.3389/fimmu.2021.687975, PMID:34276676.

[107] Yazdi ZF, Roshannezhad S, Sharif S, Abbaszadegan MR. Recent progress in prompt molecular detection of liquid biopsy using Cas enzymes: innovative approaches for cancer diagnosis and analysis. J Transl Med 2024;22(1):1173. doi:10.1186/s12967-024-05908-y, PMID:39741289.

[108] Wang HV, Chekanova JA. An Overview of Methodologies in Studying lncRNAs in the High-Throughput Era: When Acronyms ATTACK! Methods Mol Biol 2019;1933:1–30. doi:10.1007/978-1-4939-9045-0_1, PMID:30945176.

[109] Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, *et al*. Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Mol Cancer 2023;22(1):169. doi:10.1186/s12943-023-01865-0, PMID:37814270.

[110] Kase Y, Uzawa K, Wagai S, Yoshimura S, Yamamoto JI, Toeda Y, *et al*. Engineered exosomes delivering specific tumor-suppressive RNAi attenuate oral cancer progression. Sci Rep 2021;11(1):5897. doi:10.1038/s41598-021-85242-1, PMID:33723306.

[111] Ding S, Liu J, Han X, Tang M. CRISPR/Cas9-Mediated Genome Editing in Cancer Therapy. Int J Mol Sci 2023;24(22):16325. doi:10.3390/ijms242216325, PMID:38003514.

[112] Zhang J, Lin Y, Lin Z, Wei Q, Qian J, Ruan R, *et al*. Stimuli-Responsive Nanoparticles for Controlled Drug Delivery in Synergistic Cancer Immunotherapy. Adv Sci (Weinh) 2022;9(5):e2103444. doi:10.1002/advs.202103444, PMID:34927373.