Unveiling the molecular landscape: Long non-coding RNAs in neuroblastoma (Review)

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Abstract. Neuroblastoma (NB) is a prevalent malignant tumor in pediatric populations, accounting for 10-15% of childhood cancer-related deaths. Standard treatments include surgery, radiotherapy and chemotherapy; however, in recent years, immunotherapy and targeted therapies have also demonstrated encouraging outcomes, particularly for high-risk NB cases. Despite these advances, more than one-third of patients either fail to respond to immunotherapy or eventually develop therapeutic resistance, highlighting the need to further explore the molecular mechanisms driving NB and to develop novel therapeutic approaches. Notably, dysregulated long non-coding RNA (lncRNA) expression is closely associated with NB prognosis, early diagnosis and therapeutic responsiveness. The present review systematically summarizes the molecular mechanisms by which lncRNAs contribute to NB development and progression, and provides an updated overview of their emerging clinical applications as diagnostic, prognostic and therapeutic targets. The current study may offer valuable insights into the future development of lncRNA-based precision diagnostic and therapeutic strategies for NB.

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1. Introduction

Neuroblastoma (NB) ranks among the most prevalent malignant tumors in children, accounting for 10-15% of cancer-related deaths in pediatric patients (1). Notably, NB exhibits marked heterogeneity in terms of pathology, genetic alterations, biological behavior and clinical presentation. While the pathogenesis of NB remains complex, recent studies have highlighted the critical role of the MYCN gene in both its initiation and progression (2). The treatment of NB typically involves surgery, radiotherapy and chemotherapy; however, therapeutic responses vary substantially among patients owing to the intrinsic heterogeneity of the tumor. Although targeted therapies and immunotherapy have been incorporated into clinical practice, the overall treatment outcomes for patients with NB continue to be less than optimal (3). Consequently, a better understanding of NB biology and the identification of novel molecular targets are urgently needed to improve therapeutic efficacy.

Long non-coding RNAs (lncRNAs) are RNA molecules >200 nucleotides long that function as independent transcriptional units without protein-coding potential. In contrast to protein-coding genes (PCGs), lncRNAs, along with their protein-binding partners, perform intrinsic functions. These molecules serve a critical role in regulating various cellular processes, including chromatin structure, transcription, RNA stability, RNA processing, protein synthesis and RNA/protein modifications (4). Moreover, lncRNAs can function as competitive endogenous RNAs (ceRNAs) and act as molecular scaffolds for protein complexes. A growing body of evidence has indicated that lncRNAs are frequently dysregulated during tumorigenesis, where they influence both the progression of tumors and their associated outcomes. In NB, aberrant lncRNA expression has been closely associated with tumor initiation, development, metastasis and prognosis, underscoring the potential value for lncRNAs as diagnostic biomarkers and therapeutic targets in clinical settings (5).

2. Overview of NB

NB exhibits considerable variability in its pathology, biology, genetics and clinical characteristics among different patients (1-4). Unlike a number of other malignancies, some cases of NB can undergo spontaneous regression or differentiate into benign ganglioneuromas, whereas others display

highly aggressive behavior, characterized by rapid disease progression or resistance to multimodal therapeutic regimens (5-9). NB arises from the sympathetic nervous system, specifically from sympathetic adrenal progenitor cells, which possess the capacity to differentiate into adrenal chromaffin cells as well as sympathetic ganglion cells (10-15).

The transition to NB cells is influenced by multiple factors, including nerve growth factor, MYCN upregulation, SRY-box transcription factor 10 (SOX10) and mammalian achaete-scute homolog 1 genes, anaplastic lymphoma kinase (ALK) mutations and MYCN amplification. Transcription factors, such as SOX11, twist family bHLH transcription factor 1 and achaete-scute complex-like 1, also serve critical roles in the onset and progression of NB. The amplification of MYCN leads to increased levels of N-Myc protein, which has a key role in NB pathogenesis (6,7).

In addition, ALK expression is associated with a poor prognosis and, in synergy with MYCN, accelerates the growth of NB (16-22). As shown in Fig. 1, MYCN-driven oncogenic signaling reshapes the p53 pathway during chemotherapy, contributing to an initial treatment response followed by impaired p53-mediated apoptosis and eventual chemoresistance, providing a mechanistic context in which MYCN-ALK cooperation promotes aggressive disease progression. Gaining a more profound understanding of these genes and their underlying mechanisms is essential for the development of targeted therapeutic strategies.

NB is treated using a risk-stratified approach, similar to other types of cancer. Patients with low-risk NB generally receive minimal treatment, with some achieving a cure through surgery alone or undergoing spontaneous tumor regression. Individuals classified as intermediate-risk typically receive moderate-intensity chemotherapy in combination with surgical resection. By contrast, high-risk NB is most commonly treated with chemotherapy and radiotherapy (8).

The primary goal of chemotherapy is to reduce tumor burden and control metastatic disease, commonly using agents such as platinum compounds, etoposide and cyclophosphamide (23-28). Additionally, immunotherapy is being investigated as a potential treatment option for NB. While chemotherapy proves effective for some patients, approximately one-third of high-risk children with NB either do not respond adequately to it or face relapse (9). The 5-year survival rate for high-risk NB remains at <50%, with outcomes ranging from complete remission to drug resistance and severe toxicity (29-36). Given the pronounced biological and clinical heterogeneity of NB, the development of a universally effective treatment strategy remains a major challenge (37-39). The limitations of current therapies, primarily their lack of targeting specificity, highlight the need for further research into NB tumor biology and the development of novel therapeutic approaches.

3. lncRNAs

lncRNAs are RNA molecules >200 nucleotides long, serving as independent transcription units that do not code for proteins. With the advancement of high-throughput sequencing technologies, research into lncRNAs genes has increased substantially (40-44). The human genome is now annotated with >20,000 lncRNA genes, a number comparable to that of PCGs. While lncRNAs lack the ability to encode proteins, they exhibit behaviors in biological processes that resemble those of mRNA. The majority of lncRNAs are transcribed by RNA polymerase II and undergo maturation through processes such as 5'capping, 3'end cleavage, polyadenylation and splicing (45-49).

lncRNAs exhibit distinct and highly regulated expression patterns. In contrast to mRNAs, only a limited number of lncRNAs are expressed ubiquitously, whereas the majority show tissue-specific or condition-dependent expression, highlighting their functional significance. Rather than acting as templates for protein synthesis, lncRNAs and their associated protein-binding partners serve intrinsic biological roles (50-56). These molecules are involved in the regulation of chromatin organization, transcriptional control, RNA stability and processing, protein synthesis and RNA/protein modifications, and can also function as ceRNAs and molecular scaffolds. The mechanisms through which lncRNAs exert their functions are diverse, including: i) Chromatin regulation: lncRNAs interact with chromatin-modifying enzymes (such as histone methyltransferases and acetyltransferases), which influence gene expression by remodeling chromatin. For example, certain lncRNAs recruit chromatin complexes to either silence or activate target genes (57-59). ii) Transcriptional regulation, in which lncRNAs directly interact with transcription factors or RNA polymerase II to modulate gene transcription (60-62). iii) RNA stability and processing: lncRNAs regulate the stability of RNA by preventing its degradation or facilitating the degradation of specific mRNAs. Additionally, they serve a role in RNA splicing and post-transcriptional modifications, such as capping and polyadenylation (63-65). iv) Protein synthesis and modification, whereby certain lncRNAs regulate translation through interactions with ribosomes or specific proteins, and may also affect protein folding, trafficking or post-translational modification (66-68). v) ceRNA function: lncRNAs modulate gene expression by sequestering microRNAs (miRNAs/miRs), which reduces their inhibitory effects on target mRNAs. In this ceRNA mechanism, lncRNAs compete with other RNA molecules for miRNAs, thereby influencing gene regulation (69-71) (Table I).

lncRNAs are frequently dysregulated during tumorigenesis, where they act both as drivers and consequences of tumor development (72-75). Oncogenic lncRNAs are often upregulated in tumor tissues compared with in normal tissues, and their silencing frequently suppresses tumor growth or induces apoptosis. By contrast, lncRNAs with tumor-suppressive functions are typically downregulated in cancer, and their depletion tends to promote tumorigenesis. For example, activation of the lncRNA EPIC1 enhances tumorigenesis by modulating MYC target genes (40), whereas silencing of the lncRNA GAS5 accelerates cancer cell proliferation and facilitates tumor development, highlighting its tumor-suppressive role. lncRNAs are implicated not only in tumor initiation and progression, but also in metastasis and prognosis. For example, lung cancer-associated transcript 1 (LUCAT1) is markedly upregulated in both lung and esophageal cancer, contributing to tumor progression, and higher levels of LUCAT1 are associated with a poor prognosis (73). Collectively, these findings underscore the pivotal roles of lncRNAs in tumor initiation,

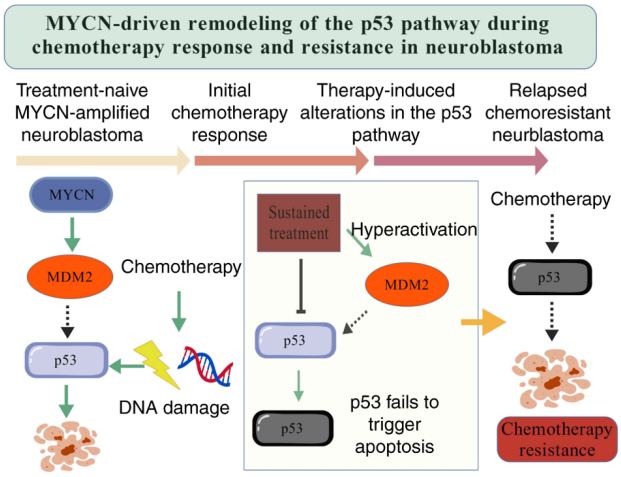

Figure 1. MYCN-driven remodeling of the p53 pathway during chemotherapy response and resistance in NB. This schematic diagram illustrates the dynamic evolution of the MYCN-p53 regulatory axis during NB progression under chemotherapeutic pressure. In treatment-naive MYCN-amplified tumors, p53 signaling remains functionally intact despite MYCN-MDM2-mediated suppression. Initial chemotherapy induces DNA damage-dependent p53 activation and apoptosis. Under sustained treatment, adaptive alterations in the p53 pathway impair apoptotic signaling, ultimately leading to chemoresistance in relapsed NB. Arrows indicate regulatory or functional associations. Green arrows represent activating or promoting effects, whereas dotted arrows indicate indirect, inhibitory or context-dependent regulatory interactions. NB, neuroblastoma.

progression and metastasis, supporting their potential utility as clinically relevant biomarkers and therapeutic targets.

4. lncRNAs affect the progression of NB

Accumulating evidence has indicated that lncRNAs serve critical roles in shaping the malignant phenotype of NB, influencing processes such as proliferation, migration, invasion, epithelial-mesenchymal transition (EMT) and programmed cell death (PCD). These effects are mediated through interactions with specific genes. As illustrated in Fig. 2, lncRNAs function through diverse molecular mechanisms, including ceRNA regulation and epigenetic modulation, thereby regulating key oncogenic pathways such as MYCN, PI3K/AKT and Wnt/β-catenin signaling. The present review summarizes current advances in understanding the involvement of lncRNAs in NB pathogenesis, with an emphasis on their molecular mechanisms and functional consequences.

lncRNAs and their role in cell proliferation and invasion. Cell proliferation and invasion are essential drivers of NB progression. Previous studies have identified several lncRNAs that serve a role in regulating these processes, contributing to the initiation and advancement of the tumor. For example, Zhao *et al* (76) demonstrated that the increased expression of the lncRNA zinc finger protein 674 antisense RNA 1 (ZNF674-AS1) is associated with poor prognosis and high-risk NB. *In vivo* experiments revealed that targeting ZNF674-AS1 expression in NB cells suppressed tumor growth. Mechanistically, ZNF674-AS1 was shown to bind to the RNA-binding protein insulin-like growth factor 2 mRNA-binding protein 3, enhancing the stability of carbonic anhydrase IX (CA9) mRNA, which leads to higher CA9 expression, thereby promoting both the proliferation and invasion of NB cells (76). In a similar study, Hsu *et al* (54) identified the lncRNA small nucleolar RNA host gene (SNHG)1, noting that its high expression is associated with a poor prognosis in NB. Silencing SNHG1 inhibited cell proliferation and invasion, and subsequent experiments indicated that the interaction between SNHG1 and HDAC1/2 modulates chromatin, thereby facilitating tumor progression (54).

Further research has highlighted the critical role of long intergenic non-protein coding RNA 1296 (LINC01296) in NB. Compared with in normal tissues, LINC01296 and tripartite motif containing 59 (TRIM59) have been found to be elevated in NB tissues, whereas the levels of miR-584-5p and miR-34a-5p are reduced. Depletion of LINC01296 was shown to suppress both cell proliferation and invasion in NB cells by functioning as a sponge for miR-584-5p and miR-34a-5p, which subsequently regulates TRIM59 expression (77). Unlike traditional studies that focus on the interactions between lncRNAs and other molecules to regulate tumor proliferation, Vaid *et al* (81) focused on the modification of lncRNAs. Their findings revealed that the lncRNA telomeric repeat-containing RNA (TERRA) interacts with the telomere region, modulating its structure and function, thus facilitating tumor progression. By facilitating m6A methylation-dependent R-loop formation, methyltransferase-like 3 can drive TERRA to target telomeres, enhancing tumor cell proliferation and invasion (78). These findings collectively suggest that lncRNAs contribute to cancer progression through interactions with proteins or RNAs, as detailed in Table II (54,76-78). However, while these studies identify lncRNAs that promote tumor proliferation and invasion, and describe their interactions with specific proteins or RNAs, they lack comprehensive evidence regarding the mechanisms through which these molecules regulate cell proliferation and invasion.

lncRNAs are found in various forms, with some promoting tumor growth and others inhibiting it. For example, Pan *et al* (94) observed a notable reduction in nuclear paraspeckle assembly transcript 1 (NEAT1) expression in NB tissues and cell lines, whereas overexpression of NEAT1 inhibited cell proliferation and invasion. Furthermore, NEAT1 was shown to interact directly with miR-183-5p, negatively regulating its expression in NB. Notably, miR-183-5p targets the 3'untranslated region (3'UTR) of forkhead box P1 (FOXP1) mRNA, reducing FOXP1 expression, and influencing cell proliferation and invasion. Additionally, FOXP1 antagonizes the effect of miR-183-5p on ERK/AKT phosphorylation, and FOXP1 small interfering RNA (siRNA) further enhances the reduction of ERK/AKT phosphorylation caused by miR-183-5p inhibitors in NB cells. This previous study progressed from initially identifying NEAT1 as a potential regulator of NB to uncovering its precise mechanistic role.

Notably, while the majority of studies on lncRNAs in NB focus on those that promote tumor growth, only a limited number of studies have identified lncRNAs that inhibit tumor proliferation and invasion, as summarized in Table II (54,60,76-96).

lncRNAs and EMT. EMT describes the biological process where epithelial cells lose their polarity and the integrity of tight junctions, adopting mesenchymal characteristics, such

Table I. Mechanisms by which lncRNAs exert their functions.

Mechanisms of action of lncRNAs	Examples	(Refs.)
Regulation of chromatin state	lncRNAs participate in chromatin remodeling and modification by binding with enzymes related to chromatin modifications (for example, deacetylases), thus affecting gene expression.	(57-59)
Transcriptional control	lncRNAs bind to transcription factors and RNA polymerase, directly influencing the transcription process.	(60-62)
RNA stability and processing	lncRNAs are involved in RNA stability regulation, binding to RNA to prevent degradation or to promote the degradation of specific mRNAs.	(63-65)
Protein synthesis and modification	lncRNAs control protein synthesis by binding with ribosomes or specific proteins.	(66-68)
Role of competitive endogenous RNA	By 'capturing' miRNAs, lncRNAs reduce the suppression of target mRNAs by miRNAs, thereby modulating gene expression.	(69-71)

lncRNA, long non-coding RNA; miRNA, microRNA.

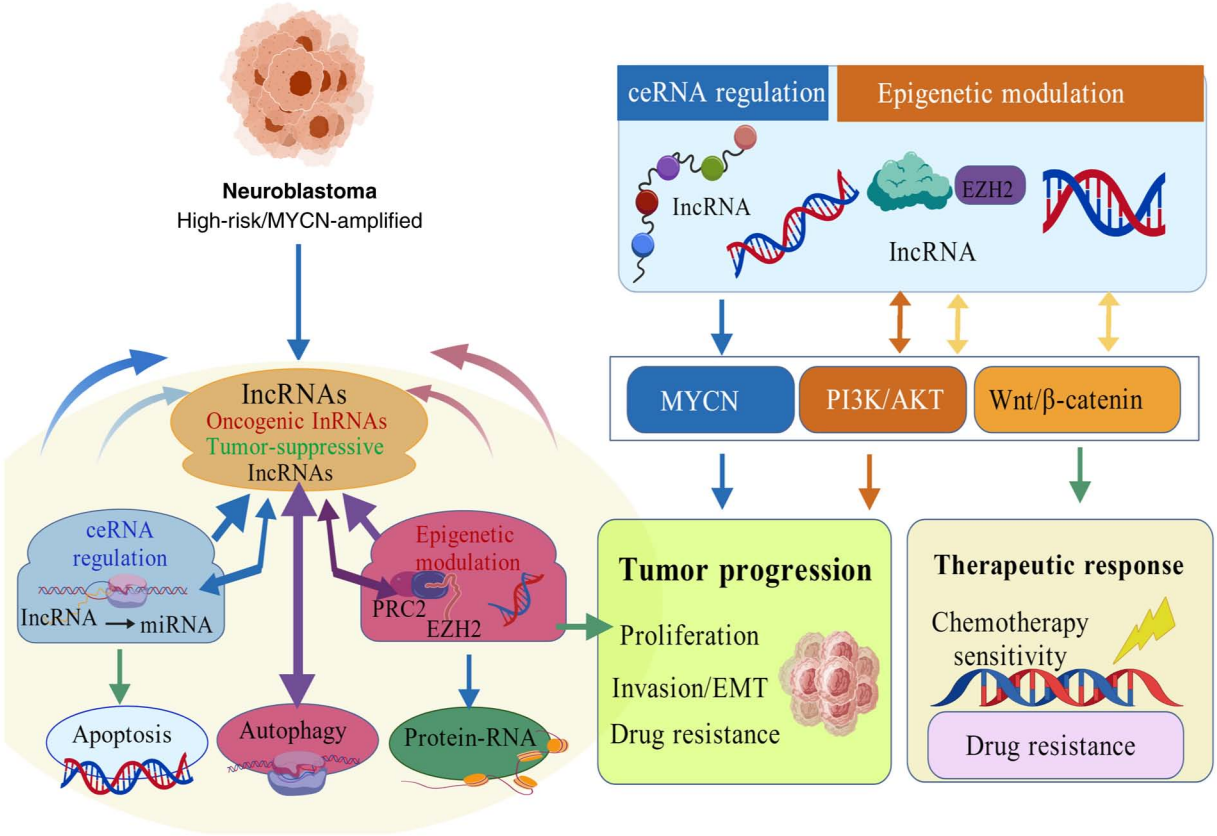

Figure 2. Graphical summary of lncRNA-mediated regulatory networks in NB. This graphical summary illustrates how oncogenic and tumor-suppressive lncRNAs regulate NB progression and therapeutic response through multiple mechanisms, including ceRNA regulation, epigenetic modulation and protein-RNA interactions. These regulatory modes converge on key oncogenic pathways such as MYCN, PI3K/AKT and Wnt/β-catenin, thereby driving tumor progression and shaping chemotherapy sensitivity, and drug resistance. Arrows represent regulatory associations rather than strict unidirectional activation. ceRNA, competitive endogenous RNA; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; lncRNA, long non-coding RNA; miRNA, microRNA; NB, neuroblastoma; PRC2, polycomb repressive complex 2.

as altered cell morphology, reduced adhesion and increased motility. EMT is a key factor in the initiation and progression of tumors, driving cellular migration and invasion, and enhancing both resistance to treatments and metastatic potential (97-100). During this transition, epithelial markers such as E-cadherin are downregulated, whereas mesenchymal markers such as N-cadherin and Vimentin are upregulated. This transition enables tumor cells to detach from the primary tumor site, invade the bloodstream and spread to distant organs, thus facilitating metastasis. EMT has been strongly linked to the

Table II. Impact and mechanisms of various lncRNAs on proliferation and invasion in neuroblastoma.

First author, year	lncRNA	Role in proliferation and invasion	Mechanism of action	(Refs.)
Zhao, 2024	ZNF674-AS1	Promotes	ZNF674-AS1/IGF2BP3/CA9 axis	(76)
Hsu, 2022	SNHG1	Promotes	Interaction between SNHG1 and HDAC1/2	(54)
Xiao, 2022	LINC01296	Promotes	Regulates miR-584-5p and miR-34a-5p to increase TRIM59 expression	(77)
Yang, 2020	SNHG4	Promotes	Regulates miR-377-3p	(78)
Wang, 2020	NORAD	Promotes	miR-144-3p/HDAC8 axis	(79)
Yang, 2021	LINC00839	Promotes	miR-338-3p/GLUT1 axis	(80)
Vaid, 2024	TERRA	Promotes	Targets telomeres	(81)
Feriancikova, 2021	MIAT	Promotes	Targets MYCN	(82)
Yang, 2020	XIST	Promotes	miR-375/L1CAM axis	(83)
Nie, 2020	DUXAP8	Promotes	Activates Wnt/β-catenin pathway via miR-29/nucleolar protein 4 like axis	(84)
Yang, 2023	AC142119.1	Promotes	Interacts with WDR5 protein and MYCN promoter	(85)
Xu, 2024	LINC00460	Promotes	miR-149-5p/DLL1 axis	(86)
Wang, 2022	LINC01296	Promotes	NCL-SOX11	(87)
Zhang, 2022	LINC00839	Promotes	miR-454-3p/NEUROD1 axis	(88)
Hu, 2020	DLX6-AS1	Promotes	miR-506-3p/STAT2 axis	(89)
Liu, 2022	LINC00839	Promotes	Recruits RUVBL1/Tip60 complex to activate NRF1	(60)
Xu, 2020	SNHG16	Promotes	miR-338-3p/PLK4 axis	(90)
Mi, 2020	LINC01410	Promotes	miR-506-3p/WEE1 axis	(91)
Jia, 2020	DLX6-AS1	Promotes	miR-513c-5p/PLK4 axis	(92)
Chen, 2021	CCAT2	Inhibits	Undefined	(93)
Pan, 2020	NEAT1	Inhibits	ERK/AKT pathway and miR-183-5p/FOXP1 axis	(94)
Tan, 2023	TUG1	Inhibits	Undefined	(95)
Zhou, 2020	CASC7	Inhibits	Targets miR-10a	(96)

lncRNA, long non-coding RNA; miR, microRNA.

invasiveness and metastatic potential of NB, influencing tumor progression and treatment outcomes (101-106). Understanding the role of EMT in NB is, therefore, essential for determining its biological behavior and developing novel therapeutic approaches. However, the mechanisms by which lncRNAs regulate EMT in NB cells remain insufficiently explored.

Ye *et al* (107) identified that the expression of the lncRNA maternally expressed gene 3 (MEG3) is markedly down-regulated in NB, with a negative association to International Neuroblastoma Staging System staging. Notably, overexpression of MEG3 was shown to induce apoptosis and inhibit EMT. Mechanistically, MEG3 and enhancer of zeste homolog 2 (EZH2) interact via a negative feedback loop that jointly promotes EMT (107). In a similar study, Ge *et al* (108) detected increased levels of SNHG16 and phosphoribosyl pyrophosphate synthetase 1 (PRPS1) in NB tissues and cells. Silencing SNHG16 could inhibit EMT, increase the proportion of cells in the G_0/G_1 phase, and reduce those in the S phase. Conversely, overexpressing SNHG16 reversed these effects. SNHG16 silencing was also able to suppress metastasis, whereas PRPS1 silencing could reduce both cell proliferation and metastasis, altering the cell cycle distribution. SNHG16 was shown to function as a sponge for miR-15b-5p, which directly targets PRPS1, and silencing miR-15b-5p or overexpressing PRPS1 mitigated the effects of SNHG16 silencing on EMT and the cell cycle. Additionally, SNHG16 knockout reduced tumor growth in xenograft models (108).

In conclusion, although EMT is essential for tumor development, the role of lncRNAs in regulating EMT in NB remains under-researched. This represents an important direction for future studies.

lncRNAs and processes related to PCD. PCD is a process in which cells undergo controlled, predetermined death via signaling pathways, which serves an essential role in maintaining both physiological functions and development. PCD comprises various forms, including apoptosis, autophagy, ferroptosis, pyroptosis and programmed necrosis (109-111).

In the context of tumors, PCD is crucial for their initiation and progression, as tumor cells often evade immune detection and therapeutic interventions by suppressing PCD, which in turn supports their survival, proliferation and metastatic capabilities. Therefore, PCD not only contributes to normal development and tissue repair, but also serves as an important therapeutic target in cancer treatment (112-115). In NB, the regulation of PCD has a notable impact on both tumor growth and metastasis. Research has shown that NB cells can bypass normal cell cycle regulation by modulating PCD pathways, thereby increasing the invasiveness and resistance to treatment of the tumor (116-120). This highlights the importance of investigating PCD in NB as it could be key to developing novel treatment strategies. For example, Li *et al* (121) revealed that the lncRNA KCNQ1 opposite chain/antisense transcript 1 could regulate miR-296-5p. The interaction between these two molecules was confirmed using RNA immunoprecipitation and biotin precipitation assays, with miR-296-5p inhibiting NB cell apoptosis *in vitro* and *in vivo*. On the mechanistic level, miR-296-5p binds directly to the 3'UTR of Bax mRNA, leading to suppression of Bax expression at both mRNA and protein levels (121). Similarly, Yu *et al* (122) revealed that elevated expression of SNHG16 is associated with poor clinical outcomes. By contrast, silencing SNHG16 can enhance apoptosis (122). Focusing on autophagy, Ye *et al* (107) discovered that MEG3 markedly inhibits cell proliferation, migration and invasion. Chromatin isolation by RNA purification analysis further suggested that the anticancer effect of MEG3 is associated with autophagy and the mTOR signaling pathway. Through LC3 fluorescence imaging and western blotting, it was shown that MEG3 reduces autophagy by inhibiting FOXO1 expression, without affecting the mTOR pathway. Mechanistically, MEG3 and EZH2 interact through a negative feedback loop to modulate autophagy in NB (107). Research into the role of lncRNAs in PCD is still limited. Although necroptosis, ferroptosis and necrosis have been linked to NB development (108-128), to the best of our knowledge, no studies have identified specific lncRNAs that regulate these processes to influence tumor initiation and progression; this represents a promising area for future research.

lncRNAs and cancer drug resistance. Tumor resistance refers to the ability of tumor cells to develop resistance to treatments such as chemotherapy, immunotherapy and targeted therapies through various biological mechanisms, which ultimately leads to reduced or completely ineffective treatment outcomes (129-132). This phenomenon has a central role in tumor progression and recurrence, as tumor cells escape therapeutic interventions by either adapting to treatment pressure or modifying their inherent characteristics, which eventually results in clinical treatment failure. NB is primarily managed with chemotherapy, targeted therapies and immunotherapy. Despite chemotherapy being the cornerstone for high-risk NB treatment, its effectiveness is often limited by its toxic effects on normal cells and the emergence of tumor resistance. Targeted therapies aim to inhibit key tumor-driving genes, such as MYCN and ALK, but resistance remains a persistent challenge in clinical settings. Although immunotherapy has demonstrated encouraging results in a subset of patients, its overall success is still hindered by the ability of the tumor to evade immune detection (133-140). Consequently, tumor resistance substantially diminishes treatment efficacy, particularly in cases of recurrent or metastatic NB, emphasizing the urgent need for innovative therapeutic strategies. Zhao *et al* (76) reported that the lncRNA ZNF674-AS1 contributes to NB cell proliferation by upregulating CA9 and preventing cisplatin-induced pyroptosis, which in turn leads to cisplatin resistance. Similarly, Xiang *et al* (141) demonstrated that NUTM2A-AS1 expression in cisplatin-resistant NB cells increases in a manner that is both time- and dose-dependent. By contrast, silencing NUTM2A-AS1 was shown to boost cisplatin sensitivity and inhibit metastatic behavior in NB cells. Additionally, the immune checkpoint protein B7-H3 was identified as a target of NUTM2A-AS1 in these cells, with NUTM2A-AS1 reducing the degradation of B7-H3 (141). In another study, Wang *et al* (79) discovered that the lncRNA non-coding RNA activated by DNA damage targets miR-144-3p to upregulate HDAC8, thereby accelerating NB progression and contributing to resistance against doxorubicin. Tan *et al* (95) explored the impact of taurine upregulated gene 1 (TUG1) overexpression on tumor immunotherapy, revealing that TUG1 knockdown markedly inhibited NB cell proliferation, colony formation and migration when compared with cytokine-induced killer (CIK) or dendritic cells co-cultured with CIK (DC-CIK) therapies alone. Furthermore, TUG1 upregulation was shown to strongly induce apoptosis and alter key molecules involved in apoptosis and EMT. After transfection with TUG1, the concentrations of IL-12, IL-2 and IFN-γ in the co-culture supernatant were markedly elevated. These findings suggest that TUG1 upregulation potentiates the antitumor effects of DC-CIK immunotherapy (95). Although previous reports have indicated that the knockdown of TUG1 can inhibit tumor cell proliferation, colony formation and migration, this study further demonstrated that TUG1 upregulation could enhance the antitumor efficacy of DC-CIK immunotherapy, exerting a synergistic tumor-suppressive effect through a gain-of-function mechanism.

lncRNA-mediated regulation of key oncogenic signaling pathways in NB

lncRNA-mediated regulation of MYCN signaling. MYCN amplification is a hallmark of high-risk NB and represents one of the most critical oncogenic drivers governing tumor cell proliferation, metabolic reprogramming and resistance to therapy. Beyond genomic amplification, MYCN expression and activity are tightly regulated at transcriptional, post-transcriptional and epigenetic levels, with lncRNAs emerging as key regulatory components.

Several lncRNAs have been shown to directly or indirectly modulate MYCN signaling. For example, MIAT acts as an upstream regulator of N-Myc, and disruption of the MIAT/MYCN axis induces cell death in MYCN-amplified NB cells, highlighting its essential role in maintaining oncogenic MYCN activity (82). In addition, AC142119.1 epigenetically activates MYCN transcription by interacting with the WDR5 protein and facilitating chromatin remodeling at the MYCN promoter region, thus sustaining MYCN-driven transcriptional programs (85).

Collectively, these findings suggest that lncRNAs function as critical modulators of MYCN signaling by either stabilizing MYCN expression or reshaping the epigenetic landscape of

MYCN target genes. Targeting MYCN-associated lncRNAs may thus represent an alternative strategy to indirectly suppress MYCN oncogenic activity in NB.

lncRNAs and the PI3K/AKT signaling pathway. The PI3K/AKT signaling pathway serves a pivotal role in NB cell survival, proliferation, metabolism and chemoresistance. Aberrant activation of this pathway is frequently observed in aggressive NB and is associated with poor prognosis (10). Emerging evidence has indicated that lncRNAs can modulate PI3K/AKT signaling through ceRNA mechanisms and transcriptional regulation.

For example, NEAT1 negatively regulates NB cell proliferation and migration by suppressing ERK/AKT phosphorylation via the miR-183-5p/FOXP1 axis. In this regulatory cascade, NEAT1 functions as a ceRNA that sequesters miR-183-5p, thereby restoring FOXP1 expression and attenuating downstream AKT signaling (94). Similarly, other lncRNAs indirectly influence PI3K/AKT signaling by regulating upstream growth factor receptors or metabolic regulators.

These observations underscore that lncRNAs do not act as isolated regulators but rather fine-tune PI3K/AKT signaling outputs by integrating miRNA networks and transcriptional control, ultimately shaping NB cell fate decisions.

lncRNAs in p53-associated cell death signaling. The p53 signaling pathway is a central mediator of DNA damage response and PCD, and its dysregulation is closely linked to chemotherapy resistance and relapse in high-risk NB. Although TP53 mutations are relatively rare at diagnosis, functional inactivation of p53 signaling frequently occurs during disease progression, where lncRNAs appear to serve contributory roles (11).

Recent studies (12,76) have indicated that lncRNAs can modulate p53-associated cell death pathways and influence therapeutic sensitivity. For example, ZNF674-AS1 promotes NB cell survival and cisplatin resistance by upregulating CA9 and inhibiting chemotherapy-induced pyroptosis, a form of PCD that intersects with p53-mediated stress responses. By suppressing cell death signaling, ZNF674-AS1 enables tumor cells to survive under chemotherapeutic pressure (76).

These findings suggest that lncRNAs may contribute to NB drug resistance by attenuating p53-dependent cell death pathways, thereby facilitating tumor persistence and relapse. Targeting p53-related lncRNAs networks could enhance therapeutic responsiveness in refractory NB.

lncRNA-induced regulation of Wnt/β-catenin signaling. The Wnt/β-catenin signaling pathway is a key driver of tumor invasion, metastasis and EMT in NB. Aberrant activation of this pathway promotes tumor cell motility and invasive behavior, contributing to disease progression and poor clinical outcomes (13).

Several lncRNAs have been implicated in regulating Wnt/β-catenin signaling in NB. Notably, double homeobox A pseudogene 8 facilitates NB progression by activating the Wnt/β-catenin pathway through the miR-29/nucleolar protein 4 like axis (84). This activation enhances EMT-associated phenotypes and increases the invasive capacity of tumor cells. Through miRNA sponging and downstream target activation, lncRNAs effectively reprogram Wnt/β-catenin signaling networks.

Together, these studies (84,85) indicate that lncRNAs act as critical upstream regulators of Wnt/β-catenin signaling, promoting NB aggressiveness and metastatic potential. Interfering with lncRNA-mediated Wnt signaling may therefore represent a promising strategy to suppress tumor invasion and dissemination.

Overall, lncRNAs participate in NB progression not merely as individual regulators but as integral components of key oncogenic signaling networks. By modulating MYCN, PI3K/AKT, p53 and Wnt/β-catenin pathways, lncRNAs orchestrate tumor growth, survival, metastasis and therapeutic resistance, highlighting their potential as novel biomarkers and therapeutic targets in NB.

5. Clinical importance of lncRNAs in NB

lncRNAs serve an essential role in the initiation, progression and prognosis of NB. Research has shown that lncRNAs exhibit distinct expression patterns in NB, where they regulate various genes and signaling pathways involved in processes such as cell proliferation, migration, PCD and resistance to chemotherapy. These regulatory activities markedly contribute to tumor growth, invasion and metastasis. The expression levels of specific lncRNAs are closely associated with the malignancy, prognosis and therapeutic response of NB, positioning them as promising biomarkers for predicting clinical outcomes and treatment effectiveness.

To provide a clearer overview of the prognostic and diagnostic relevance of lncRNAs in NB, representative lncRNAs with reported clinical significance are summarized in Table III (97-106), including their expression patterns, molecular targets or signaling pathways, associated clinical outcomes and validation status.

Su *et al* (142) developed LDAenDL, a machine learning approach that integrates deep neural networks, and LightGBM for the identification of lncRNA biomarkers in NB. LDAenDL computes the Gaussian kernel and functional similarities between lncRNAs and their disease counterparts, forming similarity networks. These networks are subsequently analyzed with graph convolutional and attention networks, facilitating the discovery of novel lncRNA-disease associations (142). Similarly, Yerukala *et al* (143) introduced support vector regression (SVR)-NB, an optimization method based on SVR, designed to identify lncRNA features related to NB survival. SVR-NB utilized data from 231 patients with NB, incorporating survival data and 783 lncRNA expression profiles from the GSE62564 database. This identified 35 lncRNA features, with a mean squared correlation coefficient of 0.85 and a mean absolute error of 0.56 years in survival time estimation. Moreover, this method ranked the lncRNAs by their predictive accuracy, selecting four key lncRNAs to predict the prognosis of NB (143).

Notably, although a growing number of lncRNAs have been associated with NB prognosis, only a subset has been validated using patient-derived samples or independent clinical cohorts, whereas a number of findings remain based primarily on retrospective datasets or experimental models.

Furthermore, RNA interference (RNAi) targeting of lncRNAs provides a potential therapeutic approach for NB. RNAi utilizes exogenous double-stranded RNA to degrade

Table III. Prognostic and diagnostic lncRNAs in neuroblastoma.

First author, year	lncRNA	Expression pattern in NB	Molecular targets/ pathways	Clinical relevance	Validation status	(Refs.)
Lamouille, 2014	ZNF674-AS1	Upregulated	IGF2BP3/CA9	Associated with poor prognosis and cisplatin resistance	Patient tumor samples; *in vitro* and *in vivo*	(97)
Dongre, 2019	SNHG1	Upregulated	HDAC/HDAC2	Associated with unfavorable survival and tumor progression	Patient cohorts	(98)
Mittal, 2018	NEAT1	Downregulated	miR-183-5p/ FOXP1	Lower expression associated with favorable prognosis	Patient samples	(99)
Taki, 2021	LINC01296	Upregulated	miR-584-5p/ TRIM59	Promotes aggressive phenotype and poor clinical outcome	Patient tissues; functional assays	(100)
Manfioletti, 2023	MIAT	Upregulated	MYCN signaling	Enriched in high-risk neuroblastoma	Public datasets; patient samples	(101)
Zhang, 2018	TUG1	Downregulated	Immune-related pathways	Associated with enhanced therapeutic response	*In vitro* and *in vivo* models	(102)
Piera-Velazquez, 2019	NORAD	Upregulated	Genome stability pathways	Linked to tumor progression	Experimental models	(103)
Lee, 2020	MEG3	Downregulated	p53 signaling	Tumor-suppressive; associated with improved survival	Patient samples	(104)
Sarrand, 2023	SNHG16	Upregulated	miR-mediated oncogenic pathways	Poor prognosis indicator	Public databases; patient cohorts	(105)
van Staalduinen, 2018	HOTAIR	Upregulated	PRC2/EZH2-mediated epigenetic regulation	Associated with advanced stage and metastasis	Patient samples	(106)

lncRNA, long non-coding RNA; miR, microRNA.

target RNA, and several studies (142-144) have utilized lncRNA short hairpin RNAs (shRNAs) delivered via viral infection for treatment purposes (144). Although no drugs targeting lncRNAs have been developed for NB, some drugs (such as ribociclib) have been found to modulate its progression by interacting with lncRNAs (145,146). Taken together, these findings highlight the translational potential of lncRNAs as biomarkers for early diagnosis, prognostic stratification and therapeutic response prediction in NB, while also underscoring the need for further large-scale clinical validation.

6. Clinical translation and therapeutic targeting of lncRNAs in NB

Although lncRNAs represent promising diagnostic biomarkers and therapeutic targets in NB, their translation into routine clinical practice remains challenging (76). Several critical barriers must be addressed before lncRNA-based therapies can be safely and effectively applied in patients.

Challenges in drug delivery, stability and specificity. One of the primary challenges in lncRNA-targeted therapy lies in efficient and tumor-specific delivery. lncRNA-based therapeutics, including antisense oligonucleotides (ASOs), siRNAs and shRNAs, are inherently susceptible to enzymatic degradation in circulation and often exhibit limited stability *in vivo*. Moreover, achieving efficient intracellular delivery, particularly nuclear localization for functionally relevant lncRNAs, remains a notable hurdle (147).

In addition, the lack of tumor-specific delivery systems may lead to insufficient accumulation at tumor sites and unintended uptake by normal tissues. This issue is particularly relevant in NB, where systemic administration of nucleic acid-based therapeutics may result in off-target distribution to healthy

organs, increasing the risk of adverse effects (147). Although viral vectors and nanoparticle-based delivery systems have been explored to improve delivery efficiency (14), concerns regarding immunogenicity, biodistribution and long-term safety persist.

Off-target effects and biological complexity of lncRNAs. Another major limitation arises from the complex and context-dependent functions of lncRNAs. Numerous lncRNAs exhibit pleiotropic regulatory roles and may participate in multiple signaling pathways across different cell types. Consequently, therapeutic modulation of a single lncRNA may unintentionally disrupt normal cellular processes, leading to off-target effects (4).

Furthermore, the tissue-specific and developmental stage-specific expression patterns of lncRNAs complicate therapeutic targeting. In pediatric tumors such as NB, unintended interference with normal developmental programs represents a particularly important safety concern (54). These factors collectively underscore the need for precise targeting strategies and comprehensive functional validation before clinical application.

Safety concerns and limitations in clinical translation. Despite encouraging preclinical data, no lncRNA-targeted therapies have yet been approved for the treatment of NB. Safety concerns remain a major obstacle to clinical translation. Potential risks include immune activation, insertional mutagenesis (in the case of viral delivery) and long-term toxicity resulting from sustained lncRNAs modulation (9).

Moreover, most existing studies rely on *in vitro* models or xenograft systems, which may not fully recapitulate the heterogeneity and immune microenvironment of human NB (148). The lack of robust clinical-grade delivery platforms and standardized evaluation criteria further limits the advancement of lncRNA-based therapeutics into clinical trials.

Future perspectives. To overcome these challenges, future efforts should focus on the development of safer and more efficient delivery systems, such as chemically modified oligonucleotides, ligand-targeted nanoparticles and tumor-specific promoters. In parallel, comprehensive toxicological evaluations and longitudinal studies are required to assess long-term safety. An improved understanding of lncRNA biology and context-dependent functions will be essential for translating lncRNA-based strategies into clinically viable therapies for NB.

7. Conclusion

A growing body of evidence underscores the pivotal roles of lncRNAs in tumor initiation and progression. Aberrant lncRNA expression has been closely associated with key oncogenic processes, including DNA damage responses, immune evasion and metabolic dysregulation in cancer cells. Depending on their biological context, specific lncRNAs may function as oncogenes or tumor suppressors, and their expression levels are associated with clinical outcomes, including disease progression and overall survival in patients with NB.

Furthermore, an increasing number of therapeutic agents have been reported to modulate NB cell proliferation, progression and drug resistance, at least in part through lncRNA-associated regulatory pathways. Collectively, these findings highlight lncRNAs as promising molecular targets for NB prognosis, diagnosis and treatment. Targeted modulation of lncRNA expression may be achieved through multiple strategies, including ASOs, RNAi, CRISPR/Cas9-based genome editing, viral delivery of lncRNA and small-molecule inhibitors. Taken together, lncRNAs represent a highly promising class of therapeutic targets for the development of molecularly guided and precision-based treatments for NB.

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Authors' contributions

ZX was responsible for the original draft preparation, research design and methodology development, and participated in the review and editing of the manuscript. ZX made the following specific contributions to the study: Conceptualization of the topic, core framework and chapter structure design of the review; developing the systematic strategy for literature searching, screening and data extraction; and independently drafting the full initial manuscript along with the figures and tables. HZ and LZ jointly reviewed and revised the paper. CW provided supervision and guidance throughout the research process. CW made decisive contributions to the conceptual framework design of the study, the interpretation of key conclusions and the revision of the final manuscript. Data authentication is not applicable. All authors commented on previous versions of the manuscript, and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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