From Diagnosis to Therapy: The Critical Role of lncRNAs in Hepatoblastoma

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Abstract

According to findings, long non-coding RNAs (lncRNAs) serves an integral part in growth and development of a variety of human malignancies, including Hepatoblastoma (HB). HB is a rare kind of carcinoma of the liver that mostly affects kids and babies under the age of three. Its manifestations include digestive swelling, abdominal discomfort, and losing weight. This thorough investigation digs into the many roles that lncRNAs serve in HB, giving views into their varied activities as well as possible therapeutic consequences. The function of lncRNAs in HB cell proliferation, apoptosis, migratory and penetrating capacities, epithelial-

mesenchymal transition, and therapy tolerance is discussed. Various lncRNA regulatory roles are investigated in depth, yielding information on their effect on essential cell processes such as angiogenesis, apoptosis, immunity, and growth. Circulating lncRNAs are currently acknowledged as potential indications for the initial stages of identification of cancer, with the ability to diagnose as well as forecast. In addition to their diagnostic utility, lncRNAs provide curative opportunities as locations and actors, contributing to the expanding landscape of cancer research. Several HB-linked lncRNAs have been demonstrated to exhibit abnormal expression and are involved in tumor-like characteristics via DNA, RNA, or protein binding or encoding short peptides. As a result, a better knowledge of lncRNA instability might bring fresh perspectives into HB etiology as well as innovative strategies for HB early diagnosis and therapy. We describe the abnormalities of lncRNA expression in HB and their tumor-suppressive or carcinogenic activities during HB carcinogenesis in this study. Furthermore, we explore lncRNAs' diagnostic and therapeutic possibilities in HB.

Keywords: Hepatoblastoma; Long non-coding RNAs (lncRNAs); Pediatric liver cancer; lncRNA therapeutic targets; Cancer diagnostics; Tumor suppression and oncogenesis

1. Introduction

Hepatoblastoma (HB) is an uncommon form of liver cancer (LvC) primarily observed in children up to the age of three, representing the most prevalent LvC within this age group. Indications of HB encompass clinical manifestations including intestinal swelling, abdominal discomfort, and weight loss [1]. Children born prematurely with very low birth weights, those with hemihyperplasia, familial adenomatous polyposis, or Beckwith-Wiedemann syndrome are at an elevated risk of developing HB [2]. Critical to the treatment of HB is comprehensive and high-quality surgery, with specialized surgeons playing a pivotal role in enhancing patient outcomes. The prognosis is promising, with a survival rate exceeding 80% when the tumor is confined to the liver and can be entirely excised through surgery following chemotherapy. However, for cases where tumors involve the entire liver or have metastasized beyond it, survival rates fluctuate between 20% and 70% within three to five years post-diagnosis [3, 4]. Notably, St. Jude stands out as the only National Cancer Institute-designated Comprehensive Cancer Center exclusively dedicated to pediatric care. At St. Jude, a specialized team of experts is committed to addressing the unique needs of children diagnosed with HB, emphasizing the institution's role as a comprehensive and specialized resource for this rare pediatric cancer [5].

The dynamic field of non-coding RNAs (ncRNAs) encompasses diverse elements, including circular RNAs (CircRNAs), microRNAs (miRNAs), and long ncRNAs (lncRNAs), all of which contribute significantly to various pathophysiological processes [6]. LncRNAs, for instance, have established themselves as significant new actors in progression of tumors, influencing critical aspects such as stemness, differentiation, invasion, and resistance to treatment. This multifaceted involvement underscores their importance in cancer-related processes [7]. MiRNAs, another subset of ncRNAs, have been extensively investigated in the cancer research landscape, with a specific emphasis on their diagnostic biomarkers value. Their intricate roles in cancer underline their relevance for diagnostic applications [8]. CircRNAs have also garnered attention in cancer field, particularly in case of lung cancer (LC). Studies exploring their implications contribute valuable understanding into the cellular processes underlying cancer genesis and progression [9]. The intricate interplay between lncRNAs and RNA-binding proteins represents a crucial avenue of exploration, particularly in the realm of cancer progression. Understanding these interactions provides a deeper comprehension of the molecular dynamics involved in cancer-related processes [10]. Moreover, the oversight functions of lncRNAs in various signaling systems in pancreatic cancer (PC), including Hippo, TGFβ/SMAD, Wnt/β-Catenin, JAK/STAT, and NOTCH pathways, have been elucidated. This comprehensive understanding sheds light on the diverse mechanisms through which ncRNAs influence cancer signaling networks [11]. The evolving landscape of ncRNAs presents a rich and diverse field of research with significant implications for the screening, predictive, and therapy of various diseases, particularly cancer. The multifaceted roles of lncRNAs, miRNAs, and CircRNAs underscore their potential as emerging actors in the complex system of molecular processes underlying cancer pathogenesis and progression [12].

LncRNAs are now recognized as critical players in oncology, exerting significant influence on gene expression control at both transcriptional and post-transcriptional levels (PTLs). These regulatory functions extend to key genes implicated in cancer development, impacting essential processes such as progression, invasion, and spread. lncRNAs offer a vital function in determining the cancerous appearance by increasing the stimulation of cancer-promoting routes and suppressing the activity of tumor inhibitors. Moreover, their involvement in drug resistance (DR) mechanisms has been recognized [13]. Acting as competing endogenous RNAs (ceRNAs), lncRNAs engage against additional RNAs for the binding of miRNAs, thereby influencing cancer-related processes. Dysregulation of lncRNAs is a recurrent phenomenon in cancer, further emphasizing their significance in cancer pathogenesis [14]. Circulating

lncRNAs became known as noteworthy indicators for early cancer detection, offering diagnostic and prognostic capabilities. Beyond their diagnostic potential, lncRNAs present therapeutic opportunities as targets and agents, contributing to the expanding landscape of cancer research [15]. In specific cancer types like colon cancer, research has focused on ferroptosis-related lncRNAs, leading to the development of prognostic models based on these lncRNAs [16]. Similarly, in ovarian cancer (OVC), lncRNAs are recognized as crucial players interacting with the tumor-suppressor protein p53, exerting critical roles in tumor initiation, proliferation, and metastasis [17]. The extensive research on lncRNAs underscores their integral role in cancer development, progression, and treatment. Their multifaceted functions, from gene expression regulation to diagnostic and prognostic potential, position lncRNAs as essential players in the intricate landscape of cancer biology.

The objective of this article is to comprehensively research and analyze the current body of knowledge concerning the involvement of lncRNAs in the pathogenesis, progression, and clinical characteristics of HB. The overarching goal is to synthesize existing research findings, providing insight into the specific lncRNAs associated with HB and their molecular mechanisms. Emphasis will be placed on understanding the regulatory roles these lncRNAs play in key cellular processes. Through achieving these objectives, the review intends to contribute to an improved perception of the intricate roles that lncRNAs play in HB. The insights gained may have significant implications for diagnosis, prognosis, and the development of therapeutic strategies for this pediatric LvC.

2. Characteristics of lncRNAs

LncRNAs constitute a class of RNA molecules exceeding 200 nucleotides that lack protein-coding functions. Their intricate involvement in an array of biological mechanism is increasingly recognized, particularly in the context of human diseases, notably cancer. Through intricate interactions with DNA, proteins, and other RNA molecules, lncRNAs emerge as pivotal regulators, influencing critical cellular mechanisms including growth, differentiation, apoptosis, and genomic stability [18, 19]. In the cancer landscape, lncRNAs play indispensable roles in crucial phenomena like epithelial-mesenchymal transition (EMT), tumor development, and immune regulation [20, 21]. Their regulatory impact extends to various cancer phenotypes, underscoring their significance in tumorigenesis. Notably, many lncRNAs have been identified as promising indicators for early cancer detection and as potential therapeutic targets, adding an extra layer to their importance in cancer research [22]. One of the primary methods by which

lncRNAs influence is by functioning as miRNA sponges, engaging in competition with miRNAs that typically regulate the expression of target mRNAs. This miRNA sponge activity has led to extensive research on the recognition and investigation of lncRNA-related miRNA sponge regulatory system in human cancer [23]. In essence, lncRNAs have emerged as versatile molecules with diverse functions, offering significant implications in various biological and disease processes. Their pivotal roles in cancer progression and tumorigenesis highlight the multifaceted nature of lncRNAs and their growing importance in the field of molecular biology and cancer research [24, 25].

2.1. Biological Functions

The regulatory roles of lncRNAs extend from normal development to pathological conditions, notably cancers. Engaging in numerous biological processes such as reprogramming pluripotent stem cells, influencing oncogenic progression, regulating the cell cycle, orchestrating X-chromosome knockdown, modulating transcriptional stimulation, interference, genetic imprinting, chromosome alterations, and nuclear transport, lncRNAs emerge as key controllers of gene expression across epigenetic, transcriptional, and PTLs [26]. Critical to understanding their importance, lncRNAs play indispensable roles in various cancer phenotypes via interaction with biological macromolecules such as DNA, proteins, and RNA (Figure 1). Their involvement spans critical cellular processes, including proliferation, differentiation, embryogenesis, and neurogenesis [18]. Moreover, lncRNAs have been recognised as influential actors in tumor growth and other human illnesses, often functioning as ceRNAs [27]. The high spatiotemporal specificity of lncRNAs positions them as pivotal regulators, contributing significantly to normal development and various disease processes, prominently including cancer. Their multifaceted roles across biological contexts underscore their emerging significance in the intricate landscape of molecular biology and disease mechanisms.

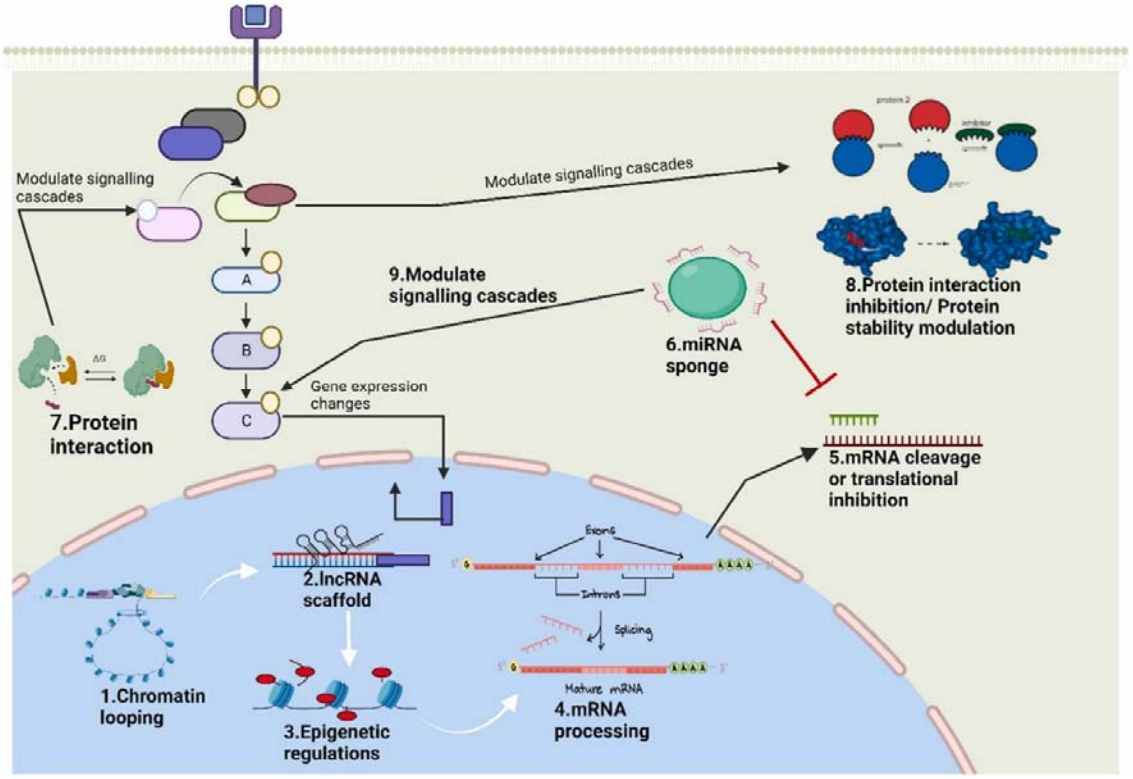

Fig. 1. The mechanisms that control lncRNA function. Generally, the subcellular positioning of lncRNAs represents their purpose, and their activities involve connections to chromatin, proteins, and RNA. Nuclear lncRNAs may either encourage or repress gene regulation by eliciting chromatin circling (1) or acting as a framework (2) to entice multiple components that control a gene locus. Nuclear lncRNAs can link epigenetic regulatory systems to the promoters of genes, causing methylation changes that regulate how genes function (3). Nuclear lncRNAs can additionally attach to mRNAs and bind regulatory chemicals, enabling them to influence mRNA processing (4). After nuclear transfer for translating, mRNAs can be linked with miRNAs that promote mRNA degradation or hinder translation, reducing mRNA performance (5). Cytoplasmic lncRNAs can act as miRNA sponges, attaching specifically the miRNAs and loosening the limitations on the mRNA (6). Cytoplasmic lncRNAs also regulate protein-protein interactions (7) and stabilization (8) to govern signaling cascades and the resulting gene expression shifts. MiRNA sponging can impact channels by changing the functionality of mRNAs (9).

2.2. Gene Regulation

LncRNAs are indispensable for preserving the equilibrium between self-renewal and lineage commitment in stem cells, ensuring proper tissue development. LncRNAs actively participate in regulating cell proliferation, differentiation, and apoptosis, positioning them as potential contributors to cancer development [26]. They perform regulatory function in gene expression

on the X-chromosome, contributing to proper dosage compensation between the X and Y chromosomes. They exhibit the capacity to either stimulate or inhibit the transcription of targeted genes, thereby exerting a critical influence on gene expression. LncRNAs participate in the process of genetic imprinting, manifesting as parent-of-origin-specific expression of certain genes [28]. They modulate chromosome structure through mechanisms like DNA methylation and histone modification, exerting control over gene expression [29]. They act as guides or scaffolds, facilitating the transport of other RNA or protein molecules between the nucleus and cytoplasm [28]. LncRNAs function as sponges for miRNAs, engaging in competitive binding with them to regulate gene expression. They play a role in genetic modulation via diverse processes, including N6-methyladenosine (m6A) alterations [30]. They exhibit diverse functionalities and their essential roles position them as key contributors to various biological processes and diseases, notably including cancer [30].

3. LncRNAs as Regulators of Signaling Pathways in Hepatoblastoma

3.1. Hedgehog (Hh) signaling pathway

LncRNAs exerting regulatory influence on Hh signaling components through various transcriptional and post-transcriptional mechanisms. The Hh cascade, integral to embryonic development and adult tissue maintenance in both invertebrates and vertebrates, has garnered therapeutic attention due to its aberrant activation in diverse malignancies, contributing to DR and apoptosis evasion [31, 32]. HB, a prevalent pediatric LvC, manifests activated Hh signaling, as evidenced by elevated transcript levels of Hh target genes such as Glioma-Associated Oncogene Homolog 1 (GLI1) and Patched (PTCH1) in tumor samples [33]. Notably, Hh interacting protein (HHIP) experiences transcriptional silencing through cytosine-phospho-guanosine (CpG) island promoter hypermethylation in specific HB cases. Management involving the DNA-demethylating agent 5-aza-2′-deoxycytidine partially restores HHIP expression. Inhibiting Hh pathway with the antagonist cyclopamine exhibits a potent suppressive influence on cell growth in HB cell lines harboring a stimulated system, eliciting a substantial increase in apoptosis [34]. In non-small cell lung cancer (NSCLC), the lncRNA BLACAT1 accelerates cancer progression by up-regulating Sonic Hh pathway activation. Elevated expression of BLACAT1 in LvC tissues, in contrast to adjacent normal tissues, is linked to increased growth, movement, and penetration. Conversely, BLACAT1 knockdown mitigates these processes, establishing its role in promoting LvC malignancy [35, 36].

3.2. MAPK signaling pathway

LncRNAs have emerged as pivotal regulators influencing various signaling pathways in cancer. Notably, in HB, the lncRNA MIR205HG has been identified as an accelerator of cell growth, movement, and invasion by triggering both the MAPK system and the PI3K/AKT cascade [37]. Meanwhile, in breast cancer (BC), the lncRNA LINC01270 exhibits a contrasting role, suppressing BC progression. This suppression is achieved through the mediation of LAMA2 promoter methylation and inhibition of the MAPK system [38]. In lung squamous cell carcinoma (LSCC), the lncRNA LINC00649 plays a promoting role by recruiting TAF15 and enhancing MAPK6 expression, thereby triggering the MAPK cascade and contributing to the development of LSCC [39]. Oral cancer presents another context where lncRNAs exert significant influence. The lncRNA DLEU2 has been identified as an accelerator of oral cancer development through the miR-30a-5p/RAP1B cascade, thereby regulating the p38 MAPK network [40]. In KRAS-mutant cancers, various lncRNAs have been implicated in interactions with KRAS, including KIMAT1, KRAS1P, LINC01420, lncRNA-NUTF2P3-001, MALAT1, Orilnc1, PART1, PCAT-1, SLCO4A1-AS1, and YWHAE. These interactions with the KRAS protein contribute to malignant transformation across diverse tissues [41].

3.3. PI3K/Akt signaling pathway

LncRNAs have established themselves as crucial actors in the regulation of the PI3K/Akt cascade within HB. Specifically, the lncRNA MIR205HG has been implicated in promoting cell growth, movement, and invasion in HB by activating both the MAPK and PI3K/AKT networks [37]. Moreover, another lncRNA, TUG1, has been found to influence angiogenesis in HB via the miR-204-5p/JAK2/STAT3 cascade, indicating its association with the PI3K/Akt signaling [42]. Additionally, research has found that the compound calycopterin exhibits anticancer effects in HB cells by suppressing the PI3K/Akt signaling and activating the MAPK system [43]. These collective findings underscore the intricate regulatory roles of lncRNAs and other compounds in regulating the PI3K/Akt system in HB.

3.4. Wnt/β-catenin signaling pathway

Research on the role of lncRNAs in HB and their regulation of the Wnt/β-catenin system is currently limited. A recent study has contributed valuable insights by focusing on the role of SOX7 in HB progression through its modulation of the Wnt/β-catenin network [44]. SOX7 expression was observed to be considerably lower in HB cells compared to nearby non-cancerous cells, while β-catenin exhibited a significant increase in HB tissues. Through

experimental interventions, such as the overexpression of SOX7 and inhibition of the Wnt/β-catenin cascade, the study demonstrated notable reductions in cell proliferation and invasion, coupled with a substantial increase in cell apoptosis as compared to the healthy category [44]. Given the encouraging results, it is critical to recognize an existing gap in research concerning other lncRNAs that may potentially regulate the Wnt/β-catenin network in HB. Further investigations are warranted to uncover additional lncRNAs involved in this pathway, therefore improving our awareness of the cellular events causing HB development.

4. Dysregulation of several key lncRNAs in HCC

LncRNAs have demonstrated significant regulatory roles in diverse signaling pathways associated with HB. GAS5 causes cell death and slows cancer development in human HB HepG2 cells. This effect is mediated through the activation of the CHOP-dependent endoplasmic reticulum stress (CDERS) network, suggesting GAS5 as a possible therapeutic approach in HB [45]. MIR205HG has been recognised to be involved in growth, movement, and invasion in HB cells by triggering the MAPK system and the PI3K/AKT cascade, suggesting its pivotal role in tumorigenesis [37]. Significantly overexpressed in HB samples and metastatic cell lines, CRNDE has been implicated in tumor growth, angiogenesis, and cell viability. Mechanistic insights reveal that CRNDE silencing exerts its anti-proliferative and anti-angiogenic effects through the regulation of the mammalian target of rapamycin (mTOR) cascade [46]. Known for its role in angiogenesis regulation, TUG1 operates through the miR-204-5p/JAK2/STAT3 cascade in HB. TUG1 knockdown has been demonstrated to inhibit HB-induced angiogenesis, with miR-204-5p recognised as a direct target of TUG1 [42]. LUCAT1 drives cell growth, movement, and invasion via miR-301b/STAT3 cascade, indicating its significant influence on these cellular processes in HB [47]. These findings underscore the essential regulatory roles of lncRNAs in numerous signaling cascade-mediated HB, presenting potential implications for therapeutic targeting and prognostic marker development in the management of this disease.

4.1. CRNDE

CRNDE has been identified as a participant in diverse cancers, such as OVC, gastric, and Colorectal cancer (CRC). Its expression is frequently elevated in cancerous cells, and multiple studies have demonstrated its involvement in fostering cellular processes, including growth, movement, and invasion, across variety of cancers [48]. CRNDE exhibits upregulation, and studies have demonstrated that its depletion leads to the suppression of cell growth, movement,

and invasion in OVC [48, 49]. CRNDE is elevated in both cancer tissues and tumor-associated macrophages in gastric cancer (GC). It serves in promoting cell proliferation in cisplatin-treated GC cells and enhances homograft tumor growth in nude mice [50]. CRC progression is influenced by CRNDE, and function substantial roles in cell growth, death, and differentiation within CRC [51]. In NSCLC, CRNDE is upregulated, and its knockdown has been shown to mitigate cell proliferation, invasion, and migration [52, 53].

LncRNA CRNDE has been implicated in HB, particularly in the regulation of angiogenesis. A study revealed that CRNDE exerts its influence on angiogenesis in HB by addressing the miR-203/VEGFA cascade. The investigation demonstrated a downregulation of miR-203 expression in HB tissues, coupled with an upregulation of CRNDE expression. Notably, the overexpression of CRNDE was established as a promoter of angiogenesis through the negative regulation of miR-203 expression [54]. Dong et al. conducted a study revealing substantial up-regulation of CRNDE in HB samples and metastatic HB cell lines. The elevated expression of CRNDE was associated with increased tumor growth and enhanced vascularity in HB through the activation of mTOR signaling as shown in Figure 2 [46]. Numerous investigations have underscored the significance of CRNDE in hepatocellular carcinoma (HCC). CRNDE functions in fostering the grwoth of HCC cells by orchestrating various pathways, involving but not only to PI3K/Akt, BCAT1, MAPK, and the Wnt/β-catenin. Moreover, CRNDE has been linked with the elevation of SIX1 expression by modulating miR-337-3p, thereby facilitating the progression of HCC [55, 56]. Additionally, CRNDE has been identified as a factor contributing to the diminished responsiveness of HCC cells to sorafenib, a commonly employed drug in HCC treatment. This reduced sensitivity is attributed to CRNDE's promotion of ATG4B-mediated autophagy, consequently mitigating the efficacy of sorafenib in HCC treatment [57, 58].

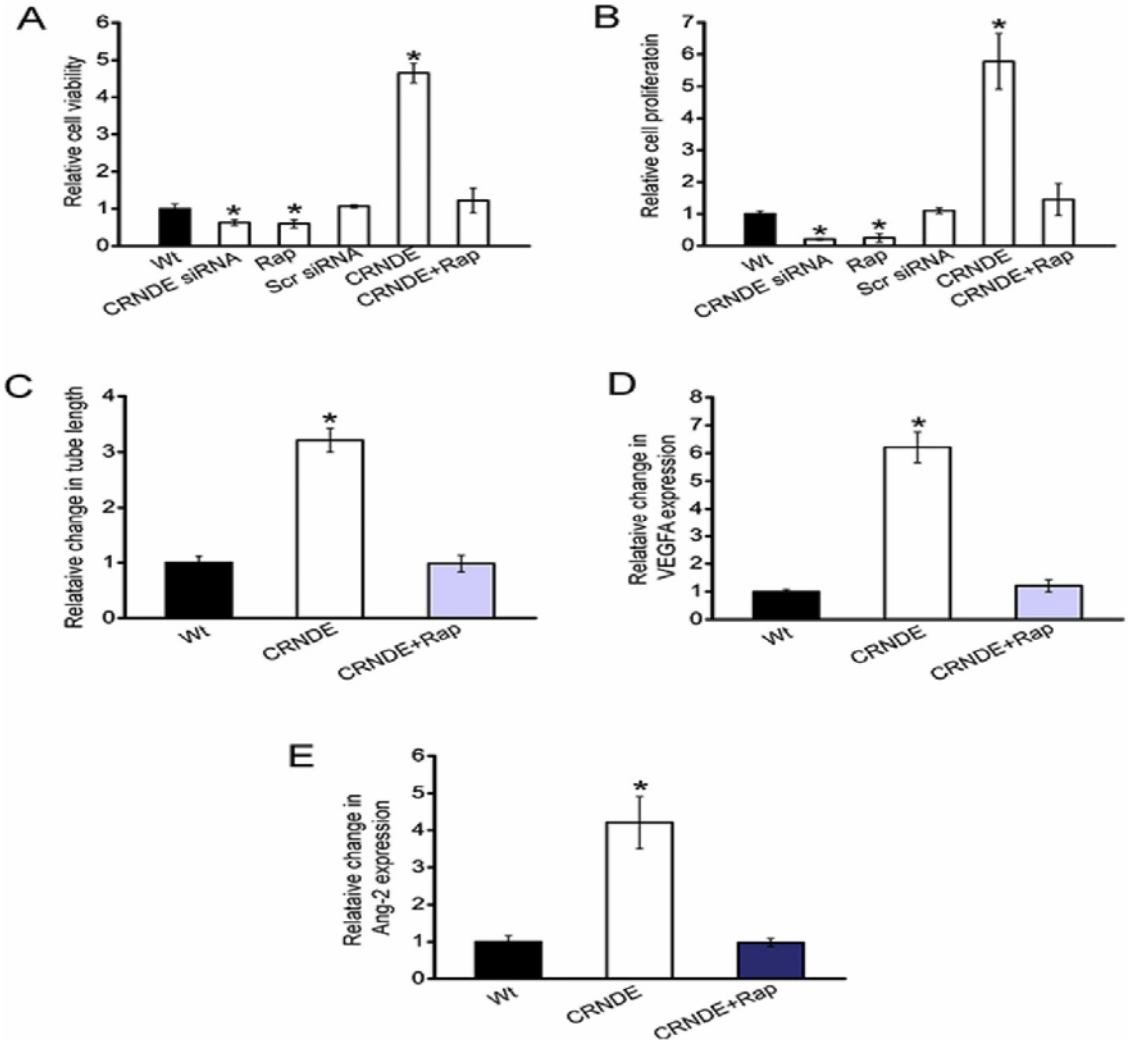

Fig. 2. The CRNDE-mTOR pathway regulatory system controls HB cell functioning and vascular impact. A, B. Scrambled siRNA (Scr), CRNDE siRNA, untreated (Wt), and overexpressed CNDE regardless of rapamycin administration were used to infect HuH-6 cells. The CCK-8 technique was used to determine the survival of cells (A; n=4; Student's t-test; P=0.0135, 0.0151, and 0.0032, respectively). To assess cell proliferation, PCNA staining and statistical analysis were performed (B; n=4; Student's t-test; P=0.0165, 0.0176, 0.0011, respectively). C-E. HUVECs were grown in matrigel-coated 24-well plates with TCM generated from HuH-6 cells infected with CRNDE, CRNDE + rapamycin therapy, or no infection, and placed in matrigel-coated wells. There was a quantitative examination of tube production (C; n=4; Student's t-test; P=0.0133).

4.2. GAS5

Growth arrest-specific transcript 5 (GAS5) has been extensively characterized as a cancer inhibitor with implications in cell proliferation and death across various diseases. Recent investigations indicate that GAS5 exhibits widespread downregulation in cancers compared to

nearby healthy tissues, and individuals with reduced GAS5 expression face significantly poorer prognoses compared to those with higher expression levels. GAS5 plays a crucial role in governing cell death, growth, spread, angiogenesis, DNA repair, and cancerous cell metabolism. In the context of COPD, GAS5 boosts pyroptosis by acting as a ceRNA, regulating the miR-223-3p/NLRP3 cascade. Given its multifaceted involvement in various cellular processes, GAS5 stands out as a potential indicator for cancer diagnosis and target for therapy [59, 60]. In a recent investigation, GAS5 has been identified as a tumor suppressor that induces apoptosis by triggering ER-stress. This occurs through the targeting of the CHOP signaling network in HB HepG2 cells [20, 45]. Another independent study reported that the reduction of GAS5 expression promotes both the proliferation of LvC cells and DR, primarily by diminishing PTEN expression [61]. Conversely, an additional investigation has shown that up-regulation of GAS5 enhances the cytotoxic effect of natural killer (NK) cells on LvC cells, and this effect is associated with the miR-544/RUNX3 pathway [62, 63]. It is evident that the role of GAS5 in HB is intricate and contingent on specific contextual factors.

4.3. LUCAT1

Lung cancer-associated transcript 1 (LUCAT1) have implications in numerous biological processes and diseases. Notably, LUCAT1 has been identified as upregulated in inflammatory conditions such as COPD and inflammatory bowel disease (IBD), with its expression positively correlated with disease severity [64, 65]. In triple-negative BC (TNBC), LUCAT1 has been recognized for its role in promoting cell stemness through a positive feedback loop involving ELAVL1, LIN28B, and SOX2 [25, 66]. Furthermore, LUCAT1 has been associated with CRC metastasis, demonstrated by its interaction with miR-133b and the EZH2 complex [67]. Additionally, LUCAT1 has been explored as a potential plasma biomarker for assessing disease activity in Crohn's disease, with elevated levels observed in patients with active disease [68]. In sepsis-induced myocardial injury, LUCAT1 has recognised as a regulator of ROCK1 expression through its interaction with miR-642a, and its knockdown has been shown to mitigate sepsis-induced myocardial cell injury [6, 69]. These diverse roles underscore the multifaceted involvement of LUCAT1 in different diseases and biological processes.

LUCAT1 has emerged as a significant contributor to HB and LvC. Investigations have revealed an upregulation of LUCAT1 in both HB tissues and cell lines, with its overexpression being strongly correlated with diminished overall survival in HB patients. Functionally, LUCAT1 has been identified as a promoter of cell growth, movement, and invasion in HB, exerting its effects

via miR-301b/STAT3 cascade [47]. Moreover, heightened LUCAT1 expression has been recognized as an independent prognostic indicator for LvC, marking an association with adverse overall survival [70, 71]. Additionally, LUCAT1 has been implicated in the promotion of immune gene expression in human macrophages [72, 73]. These collective observations propose that LUCAT1 holds promise as a possible indicator for prognosis and therapy in HB and LvC.

4.4. MIR205HG

MIR205HG, also recognized as the MIR205 host gene with diverse cancers, including HB, melanoma, esophageal carcinoma (EC), BC, and esophageal squamous cell carcinoma (ESCC). Investigations have demonstrated the overexpression of MIR205HG in HB and melanoma, contributing to enhanced cell growth, movement, and invasion. In HB, its impact involves the activation of the MAPK and PI3K/AKT system [37]. In melanoma, MIR205HG has been identified as a regulator of melanoma genesis through the miR-299-3p/VEGFA cascade [74]. Contrarily, in EC, MIR205HG impedes HNRNPA0 translation, exhibiting anti-oncogenic effects [75, 76]. Moreover, the expression of MIR205HG has been identified as a predictor of neoadjuvant chemotherapy efficacy in locally advanced BC individuals [77]. In ESCC, MIR205HG propels cancer progression by modulating the miR-214/SOX4 cascade [78]. The results presented collectively highlight the susbtantial role of MIR205HG in the initiation and advancement of various cancers, implying its possibility as a future target for therapy.

In recent investigations, MIR205HG has been identified as a key player in HB. Its involvement is associated with the acceleration of cellular invasion, migration, and proliferation within HB, a process facilitated through the activation of the MAPK and PI3K/AKT cascade (Figure 3) [37, 79]. The findings suggest that MIR205HG significantly contributes to the progression of HB and may serve as a valuable marker and potential therapeutic target for this condition.

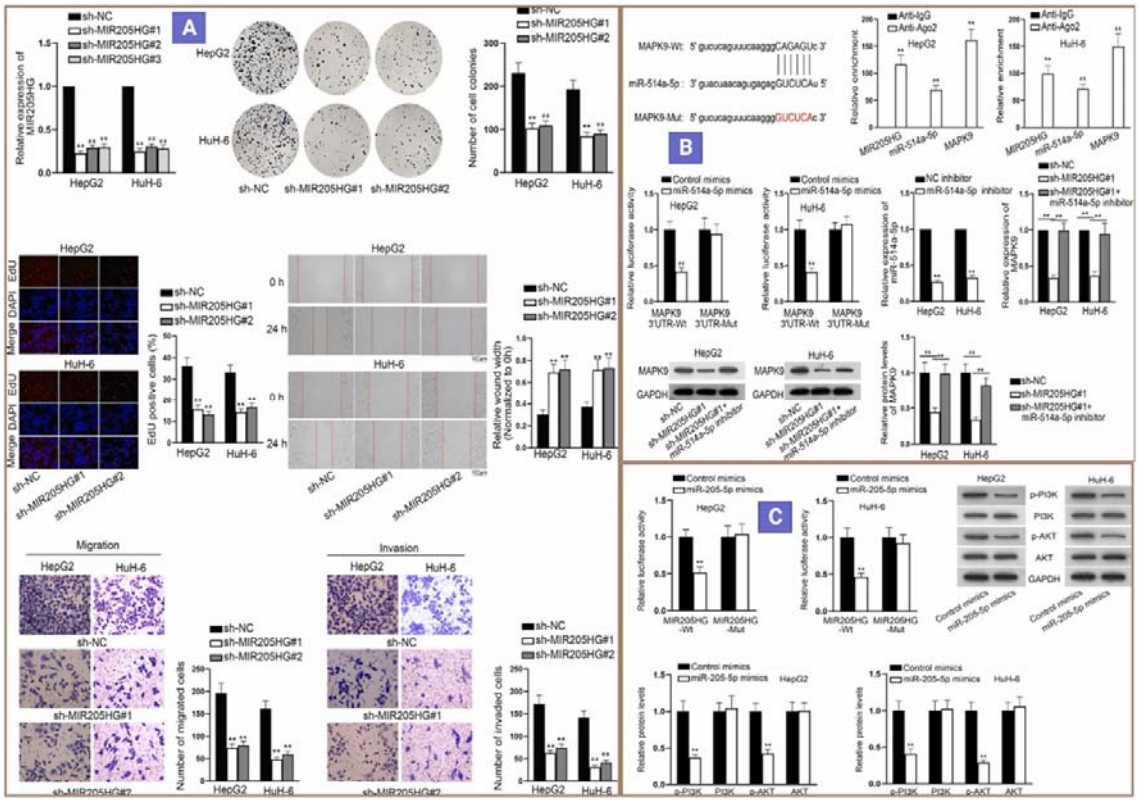

Fig. 3. MIR205HG promotes HB cell growth, movement, and infiltration (A). By attaching fiercely to miR-514a-5p, MIR205HG regulates MAPK expression and triggers the MAPK network (B). MIR205HG binds to miR-205–5p and activates the PI3K/AKT system (C).

4.5. NEAT1

Nuclear Paraspeckle Assembly Transcript 1 (NEAT1) exhibits frequent dysregulation across various cancer types and neurodegenerative diseases (NDs). It functions as a crucial structural element of paraspeckles (PSs), dynamic and membrane-less nuclear bodies influencing diverse cellular functions, notably stress response. NEAT1 plays a pivotal role in the modulation of the DNA damage repair (DDR) system, a critical component in preserving genomic stability and preventing the accrual of DNA damage, ultimately mitigating the risk of cancer and NDs. The involvement of NEAT1 and PSs in DDR has undergone extensive scrutiny, with investigations investigating their medicinal value in tumors and NDs [80, 81]. Notably, research has revealed that exosome-derived NEAT1 contributes to the exacerbation of sepsis-associated encephalopathy by promoting ferroptosis, achieved via miR-9-5p/TFRC and GOT1 system [82, 83].

NEAT1 has emerged as a significant contributor to HCC, where it exerts influence on proliferation, metastasis, and abnormal lipolysis. However, the specific role of NEAT1 in HB lacks comprehensive elucidation. Existing research has predominantly concentrated on its functions in HCC, revealing its upregulation and regulatory effects on the FOXP3/PKM2 cascade. NEAT1 has been demonstrated to promote the transcriptional activation of PKM2 and function as a molecular sponge for miR-320a, thereby impacting the proliferation, metastasis, and invasion of HCC cells [84, 85]. Hu et al. found that exosomal NEAT1 derived from HB has the capability to induce the differentiation of mesenchymal stem cells (MSCs) into tumor-supporting myofibroblasts. This induction occurs through the regulation of the miR-132/MMP9 cascade. These results not only offer valuable insights into the understanding of the underlying mechanisms in HB but also present a potential reference for clinical treatment and prognosis assessment in the future. Furthermore, the identification of this novel role of NEAT1 provides a fresh target for the development of therapeutic strategies for HB [86, 87]. While the well-documented role of NEAT1 in HCC is evident, its specific involvement in HB necessitates further exploration. Future investigations are essential to unravel the nuanced impact of NEAT1 on HB.

4.6. TUG1

Taurine Upregulated Gene 1 (TUG1) has been implicated in diverse cancers and other diseases. Its role in cancer has been subject to extensive investigation, revealing its dual nature as either a tumor suppressor or a promoter of tumor growth and metastasis, contingent on the specific context and cancer type. In the context of preeclampsia, TUG1 has been identified as a contributor to the impairment of spiral artery remodeling through engagement in a regulatory network [88]. TUG1 has been evidenced to exert influence on the progression of CRC [89]. Exosomal TUG1 originating from cancer-associated fibroblasts has been identified as a promoter of LvC cell migration, invasion, and glycolysis [90, 91]. These findings underscore the significant involvement of lncRNA TUG1 in the development and progression of diverse cancers, positioning it as a potential target for future therapeutic investigations and treatment strategies.

TUG1 is recognized for its significant involvement in HB and HCC. In HB, TUG1 exhibits a notable upregulation and has been demonstrated to facilitate tumor growth, angiogenesis, and cell proliferation, while concurrently impeding apoptosis. Investigations have highlighted the possibility of addressing TUG1 as a strategy to impede tumor growth and angiogenesis in HB,

thereby positioning it as a promising therapeutic target. TUG1's specific mode of action in HB revolves around its regulation of angiogenesis through the miR-204-5p/JAK2/STAT3 cascade (Figure 4) [42, 92]. These findings collectively suggest that TUG1 holds promise as a prospective diagnostic biomarker and therapeutic target for HB [93, 94].

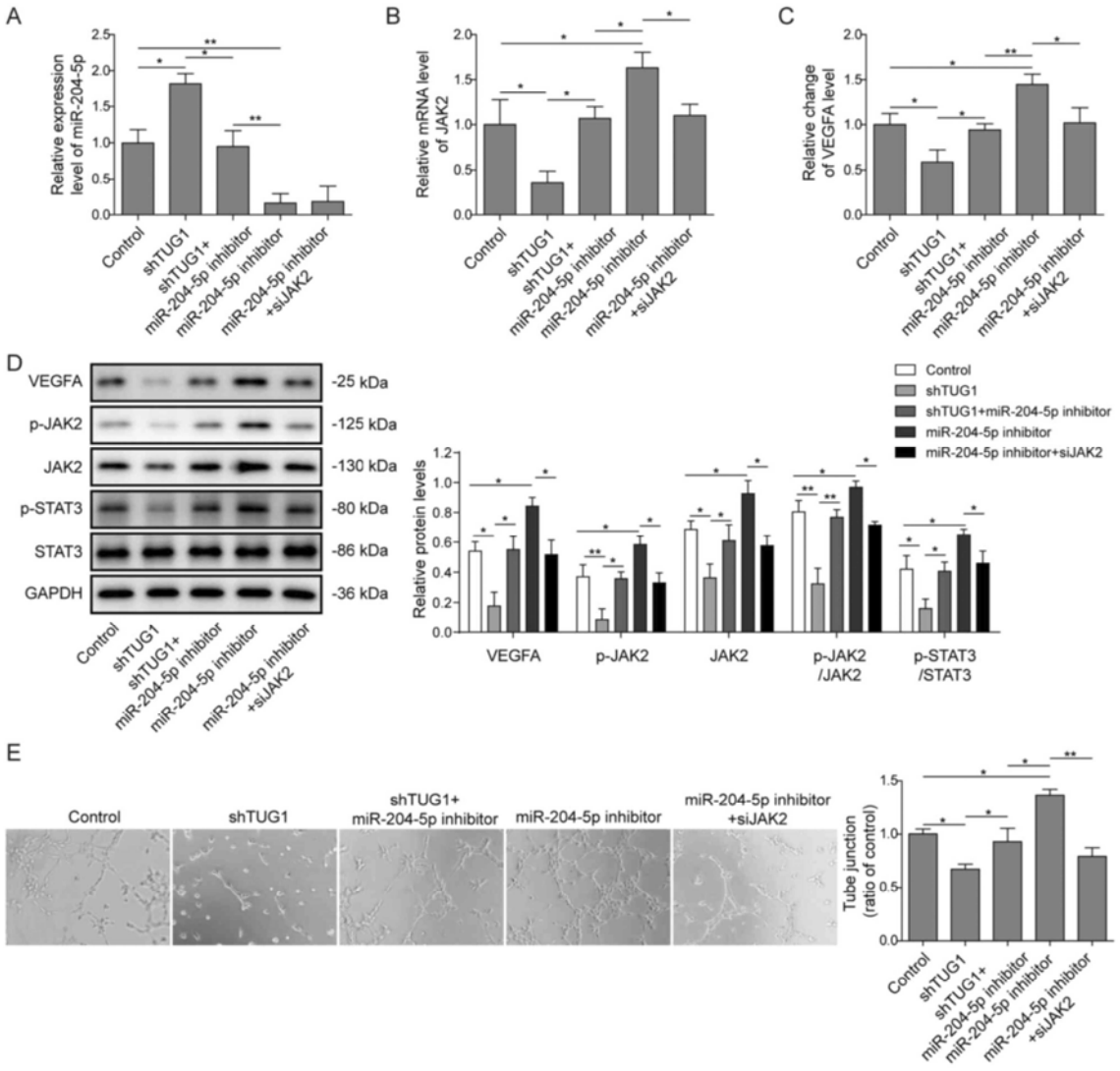

Fig. 4. TUG1 influences angiogenesis through miR-204–5p/JAK2/STAT3. HuH-6 cells were infected with an antagonist of shTUG1 or miR-204–5p, or both shTUG1 and miR-204–5p or siJAK2 and miR-204–5p. Rt-qPCR was used to determine the relative expression of (A) miR-204–5p and (B) JAK2 mRNA. (C) ELISA was used to measure the quantity of the secretory proangiogenic component VEGFA in the HuH-6 cell culture medium. (D) The Western blot method was used to determine the extent of protein expression of VEGFA, p-JAK2, JAK2, p-STAT3, and STAT3. (E) Human umbilical vein endothelial cells have been maintained in 96-well plates precoated with Matrigel and given HuH-6 cells' culture medium. Light microscopy at 100 magnification was used to acquire typical charts and tube junctions in these categories. p, phosphorylated; miR, miRNA; JAK2, Janus kinase 2; sh, short hairpin RNA; TUG1, taurine upregulated 1; si, small interfering RNA.

5. Functional Roles of lncRNAs in Hepatoblastoma

LncRNAs are being linked to several biological procedures and disorders, with a particular emphasis on their functions in oncology. In the context of HB, several research investigations have underscored the functional significance of lncRNAs in driving tumor progression. Specifically, Linc00205 has been identified as a facilitator of HB progression, exerting its influence through the regulation of the miR-154-3p/Rho-linked coiled-coil kinase 1 network, thereby engaging the MAPK pathway [95, 96]. Additionally, MIR205HG has emerged as a contributor to heightened cell growth, movement, and penetration in HB, operating through the triggering of both the MAPK and the PI3K/AKT cascade [37, 97]. Furthermore, the lncRNA HOXA-AS2 has been pinpointed as a driver of the malignant behavior of HB, showcasing its regulatory impact on HOXA3 [98, 99]. These studies collectively illuminate the diverse functional roles of lncRNAs in HB, shedding light on their participation in procedures such as promoting tumor progression and spread.

5.1. Regulation of Cell Proliferation and Apoptosis

The modulation of cell proliferation and apoptosis is a fundamental process for tissue homeostasis and is implicated in various biological phenomena, including cancer and aging. The intricate interplay between cell growth and death involves cell cycle regulators and apoptotic stimuli, and any dysregulation in these processes can lead to pathological conditions, such as cancer, NDs, and aging-related diseases. Several factors mediate the connection between cell proliferation and apoptosis, including crucial cell cycle components like c-myc, cyclin D3, p53, pRb, and E2F. These components play an indispensable role in preserving the delicate homeostasis between cell proliferation and apoptosis [100, 101]. In the context of cancer, dysregulated cell proliferation and suppressed apoptosis constitute a fundamental platform for neoplastic evolution, underscoring the significance of targeting these pivotal events for therapeutic interventions [102, 103]. The critical role of apoptosis extends to embryonic development, where it is essential for eliminating excess cells and shaping organs [104, 105]. Furthermore, apoptosis is intricately involved in the aging process, with an elevated rate observed in various aging cell populations and organs. This age-associated increase in apoptosis may serve as a protective mechanism against age-related tumorigenesis [106, 107]. The interaction of cell growth and death becomes particularly apparent in the context of DNA damage, where apoptosis and cell cycle interruption are protected are characteristic features of

cell death. The molecular connections between cell cycle advancement and proapoptotic functioning contribute to preventing the induction of apoptosis [108, 109].

HB is a form of LvC primarily observed in infants and toddlers. LncRNAs have recognised as significant actors in diverse human cancers, including HB. Although the precise functions of lncRNAs in HB continues to be elusive, several studies have provided insights into this area. For instance, one investigation revealed that the stimulation of the LUCAT1 by STAT3 facilitated migration, penetration, and proliferation in HB by modulating the miR-301b/STAT3 cascade [47, 110]. Another study demonstrated that the GAS5 induced cell death and suppressed tumor development by triggering the CDERS system in human HB HepG2 cells [45]. Furthermore, a study focused on laryngeal squamous cell carcinoma (LSCC) highlighted the dual role of lncRNAs as cancer causing or suppressing genes in onset and progression, regulating cancer via mechanisms such as epigenetic and PTLs [111]. Another review explored the involvement of lncRNAs in the angiogenic switch, a hallmark of cancer, revealing that lncRNAs performs both anti-angiogenic and pro-angiogenic function [112]. Lastly, a study identified several possible lncRNA indicators capable of distinguishing various LvC, encompassing cholangiocarcinoma (CCA), combined HCC-CCA, HCC, non-malignant HCC, and pediatric HB [98, 113].

Several lncRNAs have been identified as crucial regulators of apoptosis in HB. Liu et al. discovered that lncRNA HOXA-AS2 is up-regulated in HB. Silencing of HOXA-AS2 was associated with boosted cell death and inhibition of migration, penetration, and proliferation in HB. HOXA-AS2 elevation was found to promote malignant biological behaviors in HB. Mechanistically, HOXA-AS2 is modulated by chromatin remodeling factor ARID1B and transcription co-activator SUB1. This modulation protects HOXA3 from degradation, leading to the positive regulation of HOXA3. These findings suggest that HOXA-AS2 positively regulates HOXA3, providing insights into the participation of HOXA3 in HOXA-AS2-mediated HB oncogenesis [98, 114]. Dong et al. highlighted the significance of CRNDE overexpression in HB. CRNDE levels are substantially higher in HB samples and aggressive HB cells. Silencing of CRNDE was associated with reduced cancer progression, decreased tumor angiogenesis in vivo, and diminished survival, growth, and angiogenic effects in HB cells in vitro. Mechanistically, CRNDE knockdown exerts its anti-proliferative and anti-angiogenic influence through the mTOR network [46]. In research involving human HB HepG2 cells, GAS5 was found to induce apoptosis and inhibit cancer progression by triggering the CDERS system [45, 115]. These collective findings underscore the significant regulatory

roles of lncRNAs in HB cell apoptosis, providing potential targets for the diagnosis and therapeutic intervention in HB.

5.2. Involvement in Invasion and Metastasis

LncRNAs play pivotal roles in cancer progression, influencing crucial aspects like cell migration, invasion, and metastasis. This holds across various cancer types, including OVC, GC, BC, and PC. The multifaceted functions of lncRNAs encompass their impact on diverse biological processes, particularly those integral to metastasis-related pathways. Acting either as oncogenes or tumor inhibitors, lncRNAs emerge as promising candidates for screening, prognostic, and treatment applications in oncology. The regulatory reach of lncRNAs extends to gene expression modulation at both transcriptional and PTLs. The mechanisms through which lncRNAs exert their effects in cancer are intricate, involving epigenetic and transcriptional regulations, as well as the involvement of exosomal lncRNAs. To understand the intricacies of lncRNAs in tumor biology, there lies the potential to identify novel biomarkers that could enhance diagnostic accuracy and prognostic precision. Additionally, gaining insights into the intricate roles of lncRNAs may pave the way for innovative therapeutic approaches in oncology treatment [116-118].

HB has drawn attention for its potential association with lncRNAs, although the role of the MIR205HG has been explored in various cancers, its specific involvement in HB continues to be fully understood. Zhang et al. shed light on the impact of MIR205HG in HB, revealing its ability to stimulate movement, penetration, and proliferation through the activation of both the MAPK and the PI3K/AKT cascade (Figure 3) [37]. In various cancer types, the significance of lncRNAs in the processes of penetration and spread has been well-documented. Specifically, in NSCLC, the lncRNA LIFR-AS1 has emerged as a critical regulator, actively suppressing invasion and spread through regulation of the miR-942-5p/ZNF471 cascade [119]. Additionally, in HCC, the CRNDE has been demonstrated to exert influence on angiogenesis by acting as a ceRNAs [117, 120]. These The outcomes highlight the many responsibilities that lncRNAs play in the complex processes of invasion and metastasis across different cancer types. Despite these insights, there remains a scarcity of knowledge on the contribution of lncRNAs to invasion and metastasis in HB.

5.3. Involvement in Epithelial-Mesenchymal Transition (EMT)

Recent investigations have revealed the importance of lncRNAs. in orchestrating the regulation of EMT across various cancer types, encompassing CRC, OVC, and LC. These lncRNAs

exhibit the capacity to govern autophagy, EMT, and their intricate interplay by modulating various signaling cascades, presenting potential applications in cancer diagnosis, prognosis, and therapeutic interventions. For instance, in CRC, the prognostic implications of six and ten EMT-associated lncRNAs have been delineated, influencing the immune microenvironment, with AL591178.1 identified as a pivotal prognostic EMT-related lncRNA. Within epithelial OVC, the lncRNA SNHG10 has been revealed to elevate BIN1, thereby suppressing tumorigenesis and EMT in cancer cells through the sequestration of miR-200a-3p. In the context of LvC, the modulatory function of lncRNAs in EMT, a pivotal mechanism governing cancer cell migration and metastasis, have been elucidated. Consequently, lncRNAs emerge as promising targets for potential therapeutic strategies in cancer [121-123]. Specific investigations into the role of lncRNA in HB concerning EMT are currently limited. While extensive research has explored the impact of lncRNAs on EMT in diverse cancers such as CRC, OVC, LC, and thyroid cancer, there is a notable absence of focused studies addressing their involvement in HB-related EMT. Consequently, further research is needed to elucidate the exact contributions of lncRNAs to the control of EMT in HB.

5.4. Interaction with Tumor Microenvironment (TME) Components

Recent investigations underscore the functions of lncRNAs in orchestrating the dynamics of the TME and influencing cancer progression. These molecules exert regulatory control over the differentiation, progression, and immunosuppressive capabilities of tumor myeloid-derived suppressor cells (MDSCs) within the TME [124, 125]. Furthermore, lncRNAs emerge as critical mediators facilitating crosstalk between cancerous cells and immunity within the TME, thereby impacting both innate and adaptive immunity and, consequently, therapeutic efficacy [126]. Their association with the prognosis and immune microenvironment of diverse cancers, including bladder cancer, LC, colon cancer, papillary thyroid carcinoma, and osteosarcoma, further highlights the multifaceted involvement of lncRNAs in TME regulation [127, 128]. Consequently, unraveling the intricacies of lncRNA functions in the TME holds significant promise for identifying novel avenues in cancer treatment development.

This holds for HB where lncRNAs actively participate in TME interactions, influencing disease development. Specifically, in CTNNB1-mutated HB, the oncogenic TUG1 has recognised in promoting tumor growth. TUG1 achieves this by acting as a sponge for miR-335-5p and, consequently, modulating CXCR4-mediated infiltration of pro-tumor immunocytes [129]. A comprehensive study exploring the expression profiles of lncRNAs and mRNAs in residual

HB tissues following radiofrequency ablation (RFA) treatment revealed significant alterations in 740 lncRNAs and 663 mRNAs between experimental and untreated groups. Bioinformatics analyses highlighted the enrichment of differentially expressed mRNAs in pathways related to antigen processing, presentation of endogenous antigens, regulation of cellular metabolic processes, MAPK signaling, and cell cycle regulation. Notably, six substances were discovered as promising treatments for addressing remaining HB cells: fulvestrant, metformin, tanespimycin, MK-886, valproic acid, and wortmannin [130, 131]. This research underscores the importance of understanding the regulatory functions of lncRNAs in the TME, offering valuable insights that could serve as potential breakthrough points in cancer treatment development.

6. LncRNAs as Mediators of Drug Resistance

Limited investigations have been done on the specific involvement of lncRNAs in DR within HB. Nonetheless, existing studies indicate that lncRNAs play a substantial role in DR across various cancer types. Their interactions with diverse signaling cascades and molecular mechanisms assist in cell growth regulating, metastasis, and DR. Crucial dimensions of lncRNA-mediated DR encompass apoptosis, autophagy, cell cycle regulation, DNA repair, drug efflux, EMT, epigenetic modification, and influence on the TME. LncRNAs emerge as promising candidates for potential diagnostic, prognostic, and therapeutic indicators for cancer in general. However, a more comprehensive knowledge of the processes and clinical implications of lncRNA-associated DR specifically in HB necessitates further investigation [132, 133].

7. Future Directions and Unexplored Territories

LncRNAs have gained prominence as influential factors in diverse diseases, ranging from cancer to autoimmune conditions, positioning them as potential approach for therapy intervention. In HB, a study discerned a spectrum of lncRNAs, miRNAs, and mRNAs intricately linked with the malignant phenotypes of tumors, underscoring their candidacy as therapeutic targets [134, 135]. This paradigm extends to prostate cancer, where the regulatory influence of lncRNAs on signaling networks was identified, impacting cancer cell growth and invasion and, consequently, designating them as prospective therapeutic targets [136]. Furthermore, in the realm of rheumatoid arthritis, the perturbation of lncRNA expression was linked with the activation of pivotal cells implicated in the disease, accentuating their potential as therapeutic targets [137]. Adding to this, the identification of lncRNAs as plausible

therapeutic targets in PC stems from their involvement in both cancer initiation and resistance to therapeutic interventions [138, 139]. Hence, the therapeutic potential of lncRNAs in HB gains substantiation from their multifaceted function in the pathogenesis of numerous illnesses, including cancer.

Numerous investigations have delved into the dynamic alterations in lncRNA expression within the context of various diseases, including HB. Based on lncRNA and mRNA Expression Profiles Leveraging microarray method, an investigation scrutinized the expression patterns of lncRNAs and mRNAs in residual HB tissues following RFA therapy. Noteworthy disparities in the expression of lncRNAs and mRNAs emerged between the treated and untreated groups, offering insights into possible treatment option for residual HB cells [130, 140]. A comprehensive genome-wide investigations of lncRNA expression in HB cells brought to light 2736 differentially expressed lncRNAs, comprising 1757 upregulated and 979 downregulated lncRNAs. The investigation further identified 420 matched lncRNA-mRNA pairs and prognosticated a co-expression network involving lncRNAs and coding genes [141, 142]. An exploration into the functionality of lncRNA NBR2 in HB disclosed a substantial increase in its expression within HB tissue samples. The study illuminated the modulatory impact of lncRNA NBR2 on the growth, invasion, movement, and death of HB cells under glucose starvation, positioning it as a prospective therapeutic target [143, 144]. While these studies offer valuable insights into the potential therapeutic ramifications of lncRNAs in HB, It is critical to recognize that additional study is indispensable for an awareness of the dynamic changes in lncRNA expression and their precise roles in HB.

The incorporation of lncRNA analysis into personalized HB care is an innovative strategy aimed at enhancing the screening, prognosis, and therapy of this disease. Multiple investigations have identified differentially expressed lncRNAs in HB, elucidating their potential roles in the disease's pathogenesis. Notably, Ahmed et al. (2020) presented a computational model for inferring lncRNA-miRNA interactions, discussing its significance, methodology, and implementation [145, 146]. In a separate investigation, Zhang et al. crafted a seven-lncRNA risk signature applicable for predicting findings, immunotherapeutic reactions, and targeted treatment in clear cell renal cell carcinoma (ccRCC) patients [147]. Additionally, Burenina et al. uncovered the lncRNA HELIS as a potential biomarker for various primary LvC, including HB [148]. In the realm of personalized medicine, the involvement of artificial intelligence (AI) and machine learning (ML) has been advocated to assist physicians in tailoring the best treatment for patients based on individual genomics variants [145, 149].

This approach holds promise for expediting the utilization of genomics data and revolutionizing scientific research and clinical care. Nonetheless, full study is required to acquire a full grasp of the shifting landscape in lncRNA expression and their specific roles in HB's pathogenesis.

8. Conclusion

This comprehensive review has provided a profound exploration of HB and the dynamic field of lncRNAs in cancer biology. Shifting the focus to lncRNAs, the review has elucidated their multifaceted contributions to cancer pathogenesis, ranging from gene expression control to diagnostic biomarkers and therapeutic targets. As we navigate the complex landscape of molecular biology and cancer research, the insights presented in this review pave the route for better insight of HB and the versatile roles of lncRNAs in shaping cancer phenotypes. This comprehensive exploration contributes valuable knowledge to the fields of diagnosis, prognosis, and targeted therapeutic strategies, ultimately advancing our ability to combat pediatric LvC and other malignancies. The evolving landscape of lncRNA research in HB holds immense promise, offering potential breakthroughs in cancer treatment development as we continue to unravel the complexities of lncRNA biology.

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