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The regulation of LRPs by miRNAs in cancer: influencing cancer characteristics and responses to treatment

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Abstract
The low-density lipoprotein receptor-related protein (LRP) family is a group of cell surface receptors that participate in a variety of biological processes, including lipid metabolism, Wnt signaling, and bone metabolism. miRNAs are small non-coding RNA molecules that regulate gene expression and play a role in many biological processes, including the occurrence and development of tumors. Accumulating evidence demonstrates that LRP members are modulated by miRNAs across multiple cancer types, influencing key oncogenic processes—including tumor cell proliferation, apoptosis suppression, extracellular matrix remodeling, cell adhesion, and angiogenesis. The LRPs, miRNAs, their upstream lncRNAs, and downstream signaling molecules often form complex signaling pathways to regulate the activity of tumor cells. However, the tissue-specific roles and mechanistic underpinnings of these pathways remain incompletely understood. When examining the emerging concept of the interaction between miRNAs and LRPs, we emphasize the significance of these complex regulatory layers in the initiation and progression of cancer. Collectively, these findings are critical for advancing our understanding of the role of the LRPs family in the occurrence and development of tumors, as well as for the development of new strategies for cancer treatment.

Keywords LRPs, miRNA, Cancer, LncRNA, CircRNAs

Introduction

The low-density lipoprotein receptor-related protein (LRP) family comprises multiple members, including LRP1, LRP1b, LRP2, LRP4, LRP5/6, and LRP8. These transmembrane receptors are expressed on the cell surface and mediate diverse biological functions. Although LRPs have been extensively studied in oncology, their precise mechanisms of action in tumorigenesis remain largely elusive.

Preclinical studies suggest that LRP1 may attenuate cancer cell aggressiveness by downregulating matrix metalloproteinases (MMPs) and suppressing β-catenin signaling [1–4]. Additionally, LRP1 has been implicated in modulating cancer progression via the ERK1/2 pathway [4]. In contrast, LRP4 appears to promote tumor

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growth, migration, and invasion in gastric cancer (GC) and papillary thyroid cancer (PTC), likely through activation of the PI3K/AKT pathway [5, 6]. LRP5, a single-pass transmembrane coreceptor of the canonical Wnt signaling pathway, plays a pivotal role in tumorigenesis. By binding to Wnt ligands, LRP5 activates the Wnt/β-catenin signaling cascade through inhibition of GSK-3β, thereby promoting cell proliferation, differentiation, and epithelial-to-mesenchymal transition (EMT)– key processes driving primary tumor formation in various solid cancer [7]. Accumulating evidence demonstrates that LRP5 enhances tumorigenesis in GC [8] and in sporadic colorectal cancer [9], while also facilitating migration in ovarian cancer [10] and prostate cancer (PC) [11].

LRP6 is significantly upregulated in multiple malignancies, including hepatocellular carcinoma (HCC), retinoblastoma, breast cancer (BC), and prostate cancer (PC) [12, 13]. Similar to LRP5, LRP6 plays a crucial role in aberrant Wnt signaling activation. Furthermore, emerging evidence indicates that LRP6 contributes to cancer progression through alternative pathways, including the CXCL12/CXCR4 axis, KRAS signaling, and mTORC1-mediated regulation of oncogenic processes [14].

Notably, LRP8 overexpression has been identified across various cancer types, such as non-small cell lung cancer (NSCLC) [15], Triple-negative breast cancer (TNBC) [16], osteosarcoma [17], GC [18], ovarian cancer [19] and its elevated expression levels have been notably linked to adverse clinical and pathological characteristics as well as an unfavorable prognosis. LRP8 appears to exert its oncogenic effects through multiple molecular pathways across various tumor types. Mechanistically, LRP8 induces ERK1/2 phosphorylation to promote cell cycle progression [20], while simultaneously potentiating Wnt signaling-mediated β-catenin accumulation [21]. Additionally, LRP8 activates STAT3 phosphorylation and subsequent nuclear signaling transduction, further contributing to its tumorigenic potential [17].

MicroRNAs (miRNAs) are small non-coding RNAs that post-transcriptionally regulate gene expression through complementary binding to the 3' untranslated region (3' UTR) of target mRNAs. This interaction typically induces mRNA degradation or translational repression, effectively silencing gene expression [22, 23]. As key epigenetic regulators, miRNAs play critical roles in various cellular processes and are particularly implicated in tumorigenesis, cancer progression, and clinical outcome prediction. Notably, global miRNA downregulation has been recognized as a hallmark feature of human malignancies [24, 25]. Emerging evidence indicates that multiple miRNAs regulate LRP family members during tumor progression. However, the precise regulatory mechanisms and functional relationships between specific miRNAs and individual LRP members remain to be fully elucidated and warrant further investigation.

The roles of miRNA-regulated LRPs in gastrointestinal tract cancers

Colorectal cancer

The expression of LPR1 in colon cancer has been first discovered in 2007, It mainly expresses in stromal fibroblast and at the invasion front. With increasing tumor stages, the expression of LRP1 was decreasing in that study [26]. A reduction in LRP1 levels independently forecasts inferior overall survival (OS) and progression-free survival (PFS) in colon cancer patients [27]. It serves as a predictive indicator for the recurrence of colorectal cancer as well [28]. In contrast to normal colonic mucosa and stroma, LRP1 expression is markedly reduced in adenocarcinoma cells, a phenomenon partly attributed to mutations within the LRP1 gene. Despite the presence of numerous CpG islands in the promoter region of the LRP1 gene, the methylation status of this region remains relatively low. So, the low expression of LRP1 is not caused by methylation [27], but by other epigenetic pre-transcriptional processes such as miRNAs. In HCT116 cells, the expression of the LRP1 protein is reduced by miR-103/107 mimics, while treatment with inhibitors targeting miR-103 and miR-107 leads to the restoration of LRP1 protein levels. Doxorubicin (Dox) at lethal doses upregulates miR-103/107 through the p53 pathway, leading to the suppression of The translation of LRP1 is directly modulated by targeting its 3' UTR, which in turn results in cell death. Since LRP1 is the target gene of P53, the p53 is necessary for LRP1 expression. The p53-mediated miRNA regulatory pathway functions as a feedback loop that inhibits the translation of LRP1 transcripts, thereby promoting cell death [29]. Meanwhile, p53 can regulate HIF-1 and tumor angiogenesis through the transcriptional regulation of miR-107 in colon cancer [30]. miR-107 facilitates the growth, migration and invasiveness of colon cancer cells and suppresses their apoptosis through the miR-107-PRE3/4 pathway [31–33]. Furthermore, miRNA-107 has been identified as a downstream effector of the long non-coding RNA (LncRNA) MIR503HG [31] and circMETTL3 [33] in colon cancer (Fig. 1A). miR-103 shows higher expression levels in Pancreatic Cancers (PC) tissue than adjacent normal tissues [34]. Additionally, various research has highlighted the significance of miR-103/107 as a promoter of cancer progression [35–37]. However, some studies indicate that miR-103 may play different roles in tumor. By regulating G1/S transition, miR-103 inhibited intestinal crypt cells proliferation and survival [38]. miR-103 exhibits substantial downregulation in the blood samples of patients with early-stage colon cancer and may serve as a potential biomarker for the recurrence of this condition. miR-103 may

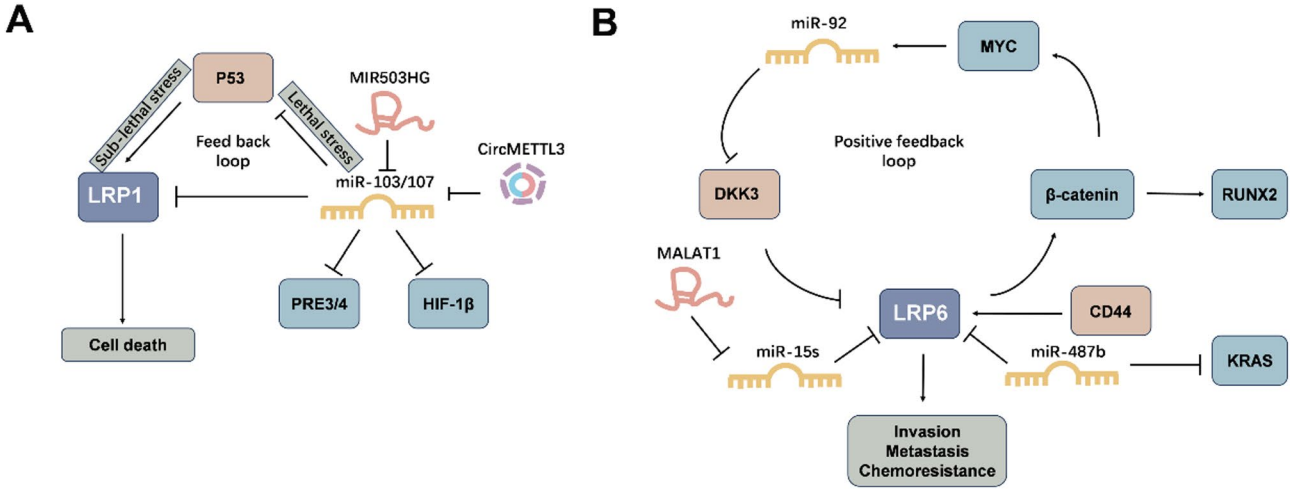

Fig. 1 The miRNA/LRPSs axis in Colorectal cancer. (**A**) Under various stress conditions, LRP1, p53, and miR-103/107 constitute a feedback regulatory loop, modulating the apoptosis of colorectal cancer cells. Oncogenic lncRNAs and circRNAs repress miR-103/107, thereby enhancing LRP1 expression. (**B**) LRP6, miR-92, and DKK3 form a positive feedback loop in colorectal cancer, synergistically with oncogenic lncRNAs, to promote LRP6 expression. This enhancement facilitates increased invasion, metastasis, and chemoresistance

play different roles in different types of specimens, which needs more experiments to prove [39].

Growing evidence underscores the pivotal function of LPR6 in colorectal cancer (CRC). Overexpression of LPR6 is observed in both colorectal cancer cell lines and in malignant human tissues [40]. LRP6 facilitates the invasive and metastatic capabilities of CRC by modulating cytoskeletal dynamics [41]. CD44 is overexpression in CRC and have a prognostic value. It is essential for the activation and proper membrane targeting of LRP6, functioning as a modulator within the Wnt/β-catenin signaling pathway [42]. LRP6 serves as a co-receptor for Wnt ligands, playing an indispensable role in the transmission of Wnt signals [43]. miR-92a has risen to prominence as a potential diagnostic indicator for CRC, as noted in reference [44]. This microRNA is known to stimulate cell proliferation [45], as well as the migration and invasiveness of CRC cells [46]. The level of miR-92a in tumor tissues correlates significantly with the likelihood of lymph node metastasis in CRC patients [47]. miR-92a induces stem cell-like characteristics in colorectal cancer cells through the stimulation of the Wnt/β-catenin signaling [48]. miR-92a induces the suppression of DKK3 through the interaction with Myc on the 3'UTR.DKK3 suppressed Wnt signaling by inhibiting the LRP6 levels. So miR-92a indirectly promoted the expression of LRP6 in CRC. LRP6, Wnt, Myc, and miR-92a are interconnected in a positive feedback loop that includes the inhibition of DKK3 in CRC [49]. It is shown that MALAT1 as a diagnostic, prognostic, metastases and therapy biomarker for CRC [50]. MALAT1 enhances the proliferation, invasion, and migration of CRC cells [51], while also diminishing their apoptosis and drug responsiveness [52], and boosting their tumorigenic potential [53] by modulating various signaling pathways and miRNAs [54]. Research has disclosed that MALAT1 is physically linked to the miR-15 family, which suppresses LRP6 expression by binding to the3'UTR of the LRP6 mRNA. This interaction augments the β-catenin signaling, resulting in increased transcription of downstream target genes such as RUNX2 [55]. miR-487b is downregulated in NSCLC tumor cell lines and reported as a Wnt inhibitors [56]. miR-487b acts as an oncosuppressor in CRC primarily by targeting key oncogenes including MYC, SUZ12, and KRAS [57]. miR-487b exerts a suppressive influence on the proliferation and invasive capabilities of CRC cells. It is found to be under expressed in CRC liver metastasis and serves as an independent prognostic indicator for 5-year OS. miR-487b diminishes the activity of the KRAS signaling pathway and curbs the WNT/β-catenin pathway by directly targeting LRP6 in CRC [58](Fig. 1B).

Pancreatic cancer

LRP1, a substantial multifunctional receptor on the cell surface, is found in pancreatic ductal adenocarcinoma (PDAC). Research indicates that elevated levels of LRP1 correlate with diminished survival rates and increased invasiveness in pancreatic adenocarcinoma [59]. It serves as a receptor for eHSP90α, facilitating its role in promoting metastasis through the activation of the AKT signaling pathway [59, 60]. In pancreatic cancer, PAI-1 enhances the malignant phenotype of cancer cells through the LRP-1/ERK/c-JUN pathway [61]. Other studies have reported the tumor inhibitory effect of LRP1. For instance, the reduction in expression of the MIF has been shown to slow the growth of PDAC cell xenografts and to suppress cell proliferation under both

normoxic and hypoxic conditions. This regulatory effect is mediated by the MIF-p53-LRP1-uPAR signaling.

miR-429 belonged to miR-200 gene family it is located in the hypermethylated region of chromosome 1, and is low expressed in a variety of tumor cells [62]. Numerous investigations have uncovered the modulatory function of miRNA-429 in PDAC. miR-429 can be related to poor outcome of PDAC patients [63, 64]. miR-429 significantly suppresses cell viability and invasion of the PaCa-2 and BxCP3 cells by NT-3 [65]. miR-429 also suppresses the growth of PANC1 and SW1990 cell lines in vitro by directly targeting TBK1 [64]. miR-429 is negatively regulated by OIP5-AS1. It suppressed PDAC cell growth, migration and reversed EMT process by targeted to FOXD1 and inhibited ERK pathway [66, 67]. LRP1 were predicted to be target genes of miR-429 in PDAC [63]. As a gene targeted by miR-429, LRP1 could potentially serve as a biomarker for the clinical diagnosis of PDAC (Fig. 2A).

LRP5 is a surface protein on cells that facilitates the internalization of ligands. It plays a role in enhancing the canonical Wnt signaling pathway within cells and is crucial for insulin secretion triggered by glucose [68–70]. LRP5 has been proved overexpressed in metastatic pancreatic endocrine neoplasms as compared with non-metastatic pancreatic endocrine neoplasms [71]. LRP5/6 has been recognized as a target substrate for CDK14 in vivo [72]. The expression of CDK14 is notably increased in PDAC tissue samples. Phosphorylation of LRP5/6 by CDK14 is a crucial factor in the activation of the Wnt signaling pathway. In PDAC, miR-26b directly targets CDK14, suppressing its expression, along with the expression of phosphorylated LRP6. This leads to a reduction in the aggressiveness of cancer cells and a decrease in tumor growth both in vitro and in vivo [73]. miR-194 suppresses the expression of CDK14 by directly targeting it, thereby significantly reducing the protein levels of phosphorylated LRP6. This action results in the modulation of PDAC cell proliferation and migration [74]. Concurrently, the H19 modulates miR-194, which in turn has an antagonistic effect on the aforementioned factors. miR-194 has been correlated with the overall survival rates of pancreatic cancer patients [75, 76]. In contrast to the aforementioned research findings, overexpression of miR-194 may promote tumor growth and local invasion in an orthotopic pancreatic cancer mouse mode [77] (Fig. 2B). At present, there is no research to confirm whether LRP5/6 is directly regulated by miR-194 or miR-26b, and the role of miR-26b, miR-194 and LRP6 in pancreatic cancer still require further investigation.

Significant increases in FGD5-AS1 expression is observed in Pancreatic Cancers [78]. Elevated levels of FGD5-AS1 expression are associated with an unfavorable prognosis in patients with Pancreatic Cancers. FGD5-AS1 exhibits tumor promoting activities by activated STAT3/NF-κB signaling pathway [79]. FGD5-AS1 promotes cell proliferation and migration by sequestering miR-520a-3p [80]. FGD5-AS1 functions as a competing endogenous RNA (ceRNA) to enhance the expression of BHLHE40 through the interaction with miR-15a-5p in Pancreatic Cancers cells. BHLHE40, in turn, promotes the proliferation, migration, and apoptosis of these cells [81]. In Pancreatic Cancers, miR-577 serves as a downstream target of FGD5-AS1. It counteracts the proliferative effects of FGD5-AS1 by binding to the 3'UTR of the LRP6 gene, thereby modulating the Wnt/β-catenin signaling pathway [82]. Furthermore, miR-577 can be absorbed by LINC01094, which stimulates the proliferation and metastasis of PDAC both in vitro and in vivo by activating the PI3K/AKT signaling pathway [83]. circRNA_0007334 competitive adsorbs miR-577 to enhance the migration ability of pancreatic ductal adenocarcinoma cells [84]. Previous research has indicated that miR-454 can act as either an oncogene or a tumor suppressor, depending on the cancer type. In the case of HCC, miR-454 has been shown to enhance cell proliferation, invasion, and EMT. Additionally, miR-454 stimulates the growth of tumors engrafted with HepG2 cells in vivo. Thus, in the context of HCC, miR-454 behaves as an oncogene [85]. miR-454 stimulates the proliferation and invasion of PC cells by activating the WNT/β-catenin signaling pathway [86]. Conversely, miR-454 has a potent effect in reducing tumor weight and volume in vivo by disrupting the Wnt signaling pathway in ovarian cancer [87]. It inhibits the proliferation and invasiveness of ovarian cancer cells by targeting the E2F6 gene [88]. miR-454 functions as a suppressor in tumor growth, angiogenesis in PDAC, by inhibiting Wnt/β-catenin signaling through targeting LRP6 [89](Fig. 2C). Moreover, miR-454-overexpressing formed significantly less PDAC lung metastases than control cells.

C. Oncogenic lncRNAs and circRNAs diminish the suppressive effects of tumor-suppressor miRNAs on LRP6, thereby promoting LRP6 expression and enhancing cell proliferation, metastasis, and angiogenesis.

Hepatocellular cancer

While a growing body of research suggests a link between LRP1 and cancer progression, the exact function and specific mechanisms by which it influences various cancer types remain subjects of ongoing discussionFurther research is required to understand the role of LRP1 in HCC. Existing studies have indicated that reduced LRP1 levels are correlated with a poor prognosis for HCC patients following curative surgery. The suppression of LRP1 is found to increase the expression of MMP9, which in turn boosts the migration and invasiveness of HCC cells in vitro and escalates the rate of pulmonary

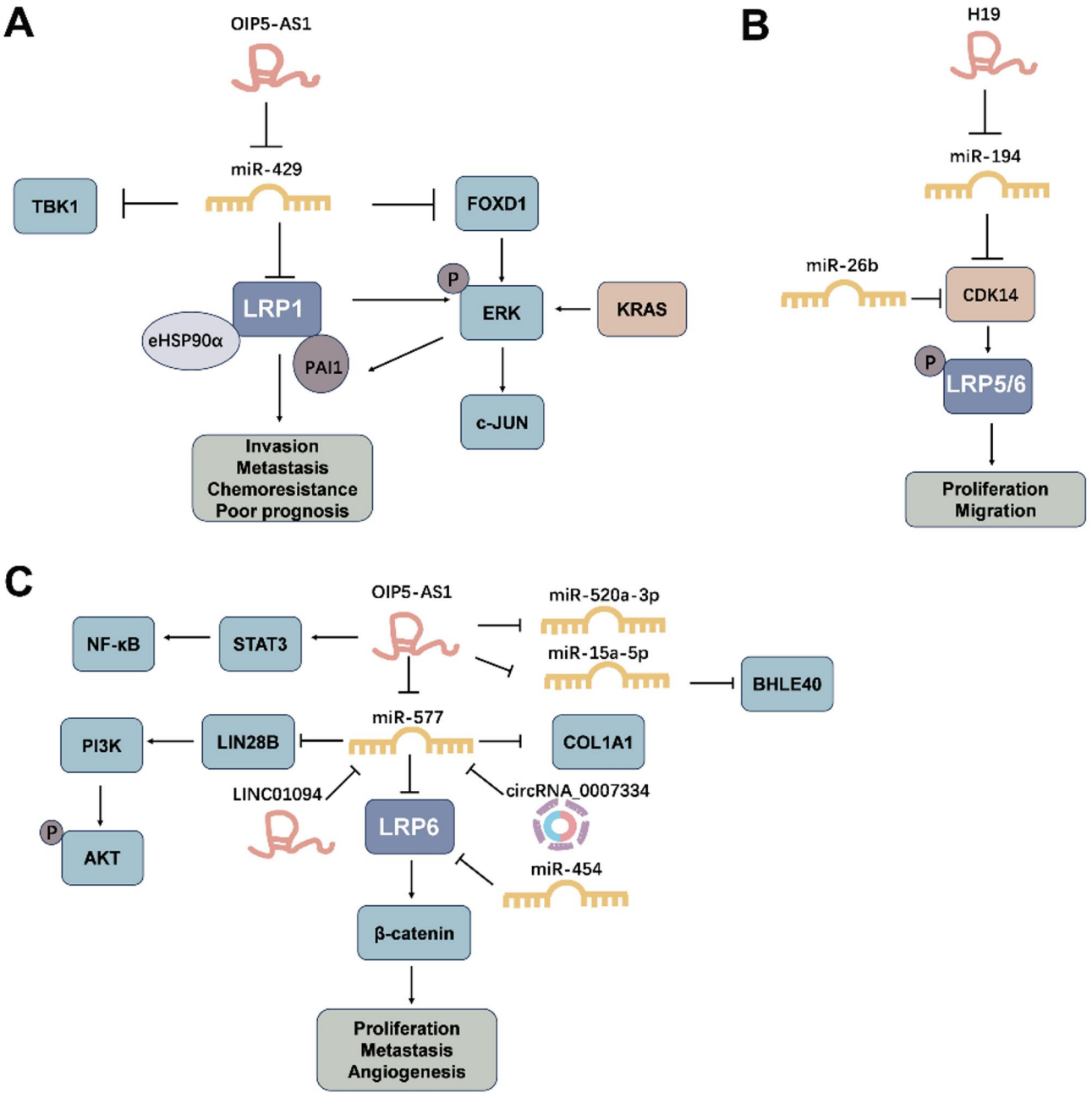

Fig. 2 The miRNA/LRPSs axis in Pancreatic cancer. (**A**) OIP5-AS1 upregulates LRP1 expression by inhibiting miR-429, thus augmenting invasion, metastasis, and chemoresistance in pancreatic cancer. (**B**) H19 enhances LRP5/6 expression by suppressing miR-194, leading to increased proliferation and migration in pancreatic cancer

metastasis in liver orthotopic tumors [3]. Previous study have reported that over expression of LRP4 is found in both HCC patients and a range of HCC cell lines. Moreover, LRP4 depletion also significantly reduces cellular proliferation and invasion ability [90]. overexpression of LRP4, is significantly associated with T stage, pathologic stage, vascular invasion, and poor prognosis for patients with HCC [91]. LRP4-MuSK signal is required in Agrin induces activation of YAP, and promoted liver cancer development [92].

Oncogenic function of lncRNA HUMT is revealed in TNBC. It is a metastasis-associated lncRNA and predicts poorer clinical prognosis [93, 94]. High expression of miR-455-5p significantly correlates with better overall survival in HCC tissues and blood exosomes [93]. miR-455-5p has the capability to inhibit tumor growth, colony formation, as well as the migration and invasiveness of

cancer cells by disrupting the IGF-1R/AKT/GLUT1 pathway. The reduction expression of miR-455-5p linkes to poorer patient outcomes [95]. lncRNA HOXA-AS3 promotes the proliferation, migration, and invasion of HCC cells, modulates the cell cycle, and suppresses apoptosis via the regulatory axis involving miR-455-5p and PD-L1 [96]. Intriguingly, research has uncovered that HUMT, which is overexpressed in HCC, functions as a miRNA sponge for miRNA-455-5p, leading to an increase in LRP4 levels and thus facilitating the proliferation and metastasis of HCC [97](Fig. 3A).

Likewise, the stimulation of the Wnt/β-catenin pathway plays a crucial role in the development of hepatocellular carcinoma HCC. As the upstream of LRP6 receptor interacts with FZD family which have seven transmembrane receptors to activate the Wnt/β-catenin pathway, LRP6 may play a role in hepatocarcinogenesis through hyperactivation of the Wnt/β-catenin pathway. LRP6 is found to be overexpressed in HCC, and its stable overexpression in HCC cells leads to enhanced cell proliferation, migration, and invasion both in vitro and in vivo [98]. Elevated levels of LRP6 expression are linked to the aggressive characteristics and unfavorable outcomes in HCC. CCN2 binds with LRP6 and enhances the invasiveness, migration, and proliferation abilities in HCC through upregulating phosphorylation level of LRP6 [99]. Research has identified that ABCG1, an ATP-binding cassette transporter that facilitates tumor cell migration and invasion, is modulated by the LRP6-Wnt/β-catenin pathway in HCC [100]. Stimulation of the LRP6-Wnt/β-catenin pathway results in elevated levels and activity of FRMD5, a protein that plays a pivotal role in the growth, mobility, tumor formation, and spread of HCC cells [101].

It is found that miR-1269a is deregulated in HCC [102]. miR-1269a is a signature for differentiating HCC patients from the healthy control [103]. Survival analysis of clinical samples shows that miR-1269a is associated with prognosis in HCC [104]. miR-1269a suppresses the proliferation of HCC cells and induces apoptosis by repressing the expression of its target gene, LRP6 [105]. Decreased expression of miR-202 correlates with tumor dimensions, vascular invasion, and the TNM staging in HCC patients, as well as with diminished overall survival rates. miR-202 is capable of curbing cellular glucose uptake, lactate generation, and proliferation by targeting the gene HK2 [106]. miR-202 significantly inhibits cell proliferation, migration, invasion and EMT, as well as induced apoptosis and cell cycle arrest and prevented tumor formation in vivo by downregulating BCL2 expression [107]. Furthermore, miR-202 hinders the proliferation, tumorigenic potential, and cell cycle advancement in HCC cells by directly targeting LRP6 [108]. Research has shown that miR-432 levels are negatively associated with the expression levels of β-catenin and LRP6. By directly targeting the 3' UTRs of LRP6, miR-432 reduces the activity of the Wnt/β-catenin pathway, thereby significantly inhibiting the proliferation of HCC cells [109]. A deficiency in miR-610 is observed in HCC cells and tissues, and this deficiency correlates with the survival rates of HCC patients. The downregulation of miR-610 reduces Wnt/β-catenin signaling by directly inhibiting LRP6, which in turn enhances the proliferation and tumorigenic capacity of HCC [110].

A multitude of studies have substantiated the oncogenic function of TMPO-AS1 in various types of cancer. TMPO-AS1 acts as an enhancer of the aggressive characteristics of HCC cells by sequestering miR-320a

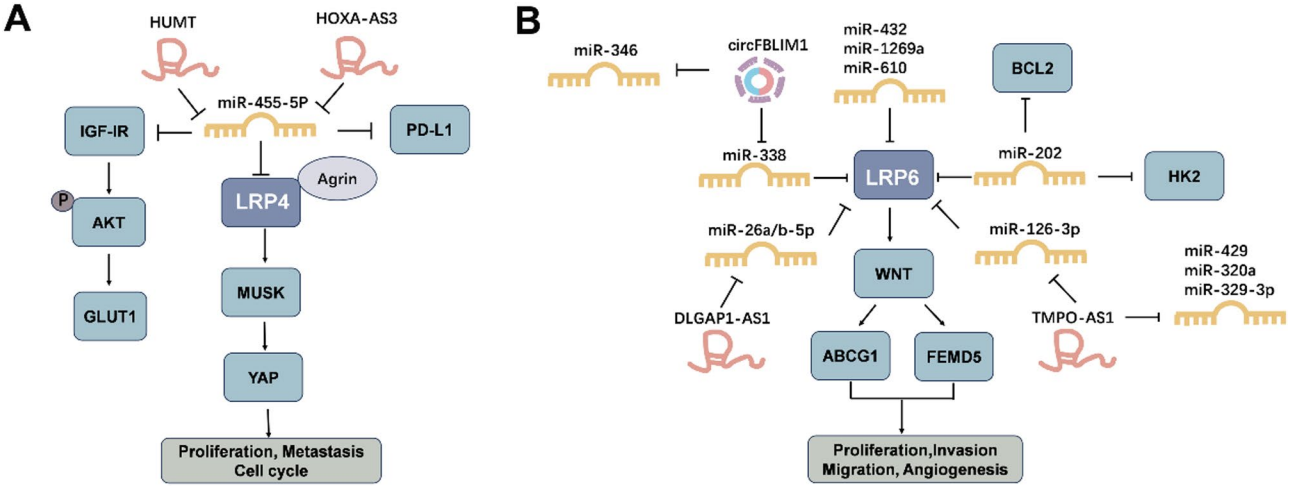

Fig. 3 The miRNA/LRPSs axis in Hepatocellular cancer. (**A**) LncRNAs stimulate the expression of LRP4 by suppressing miR-455-5p, which in turn promotes cell proliferation, metastasis, and cell cycle progression in hepatocellular carcinoma. (**B**) Multiple miRNAs have been identified to negatively regulate LRP6 in hepatocellular carcinoma. Oncogenic lncRNAs and circRNAs counteract these miRNAs, increasing LRP6 expression and thereby promoting cell proliferation, invasion, metastasis, migration, and angiogenesis

[111], miR-429 [112] and miR-329-3p [113]. TMPO-AS1 promotes HCC proliferation, metastasis, and EMT by increasing LRP6. Additionally, TMPO-AS serves as a miRNA sponge for miRNA-126-3p, thereby activating the miR-126-3p/LRP6/β-catenin pathway [114]. Being a direct target of miR-126-3p, the protein levels of LRP6 exhibit an inverse relationship with the expression of miR-126-3p, and it stimulates the metastasis and angiogenesis of HCC both in vitro and in vivo [115]. DLGAP1-AS1, functioning as a molecular sponge for miR-26a-5p and miR-26b-5, has been shown to contribute to the growth and metastasis of HCC. The target inhibitory effect of miR-26a/b-5p on LRP6 is reversed by DLGAP1-AS1. DLGAP1-AS1 facilitates the progression of HCC and EMT by positively modulating the activity of the Wnt/β-catenin pathway through LRP6 [116].

circFBLIM1 is upregulated in HCC, which may inhibit growth and invasion, and promote apoptosis in HCC through sponging miR-346 [117]. circFBLIM1 is also over expressed in HCC serum exosomes and HCC cells. It accelerates the advancement and glycolytic activity of HCC by serving as a sponge for miR-338, thereby leading to an upregulation of LRP6 [118](Fig. 3B).

Gastric cancer

LRP4 exhibits elevated expression in gastric cancer (GC) and is associated with an unfavorable prognosis for GC patients. It enhances the migration, invasion, and EMT of GC cells by modulating the PI3K/AKT signaling pathway. LRP4 serves as a direct target for miR-140-5p, and its levels are inversely associated with the expression of. miR-140-5p in GC tissues [6]. The expression of miR-140-5p is notably reduced in GC tissues, and its levels are correlated with lymph node metastasis, TNM stage, and diminished overall survival rates in GC patients [119, 120]. miR-140-5p suppresses the proliferation and invasive capacity of GC cells by reducing the expression of WNT1 and β-catenin, and by directly targeting the 3'UTR of the YES1 gene [119]. miR-140-5p is potentially implicated in the mediation of resistance to 5-FU in GC via the regulatory axis involving SNHG20/miR-140-5p/NDRG3 [121](Fig. 4A).

Polymorphisms in the LRP5 gene are linked to an unfavorable prognosis and diminished response to first-line chemotherapy with the EOF regimen in individuals suffering from advanced GC [122]. LRP5 promotes proliferation, invasion, migration and EMT in vitro in GC cell through Hsp90ab1-LRP5 interaction, thereby activates of the AKT and Wnt/β- catenin signaling pathways [123]. LRP5 is found in higher concentrations in GC tissues and shows a positive correlation with the progression to advanced clinical stages and a poorer prognosis. It boosts the proliferation, invasiveness, and drug resistance of GC cells by activating the Wnt signaling pathway and promoting aerobic glycolysis [8, 124]. The expression of the long non-coding RNA SBF2-AS1 is elevated in

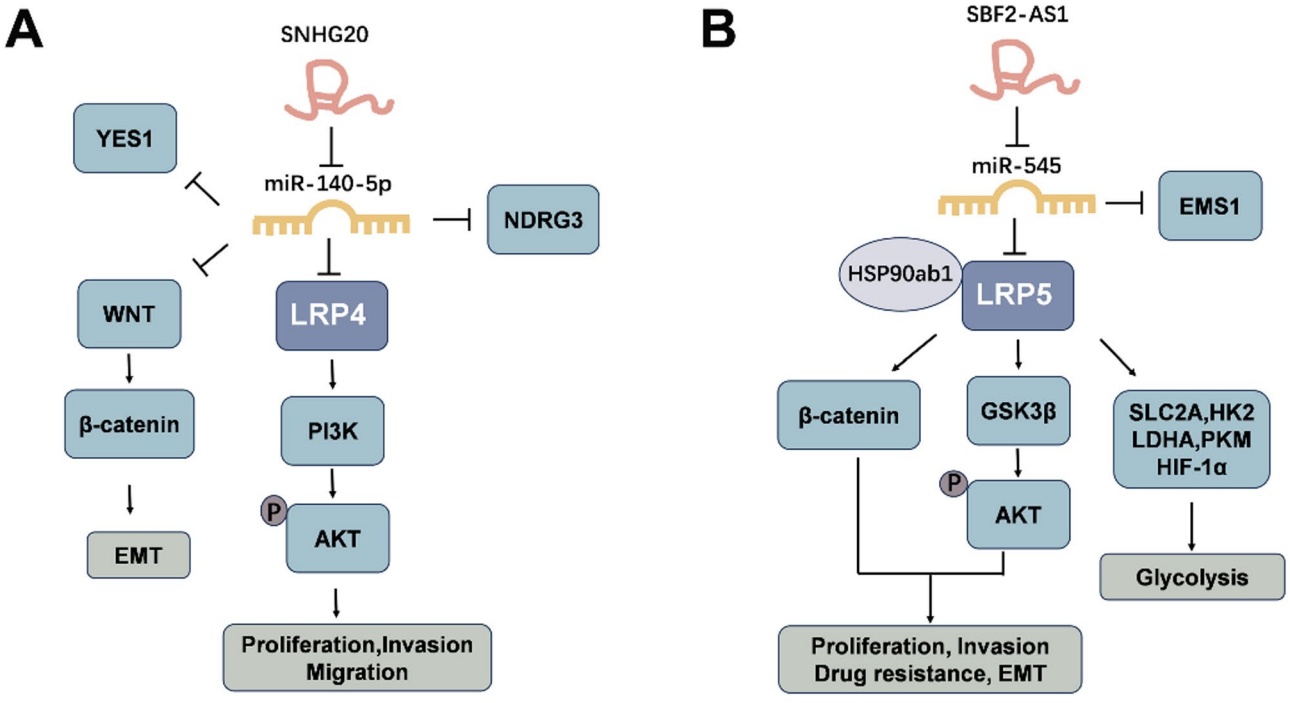

Fig. 4 The miRNA/LRPSs axis in Gastric cancer. (**A**) SNHG20 promotes LRP4 expression by suppressing miR-140-5p, enhancing proliferation, invasion, and migration in gastric cancer. (**B**) SBF2-AS1 enhances LRP5 expression by inhibiting miR-545, thereby promoting proliferation, invasion, EMT, and drug resistance in gastric cancer

GC tissues and is associated with more advanced clinical stages and a lower survival rate. SBF2-AS1 promotes GC progression via targeting miR-545/EMS1 pathway [125]. While another study shows that miR-545-3p could have a suppressive effect on osteogenesis via targeting LRP5 [126]. Intriguingly, in vitro SBF2-AS1 knockdown inhibits the Wnt/LRP5 signaling pathway [124](Fig. 4B).

Abnormal LRP8 expression have also been associated multiple digestive system tumors. An overabundance of LRP8 in Huh7 cells leads to a decrease in apoptosis and is a contributing factor to the resistance of HCC cells to sorafenib treatment [127]. LRP8 is high expression in pancreatic cancer, and contributed to cell cycle and cell proliferation through activating ERK1/2 pathway [20]. The antimigratory role of MPA is achieved through down-regulation of LRP8 in gastric cancer cell [128]. Furthermore, miR-142 suppresses the proliferation, migration, invasion, and EMT of GC cells in vitro, as well as tumor growth in vivo, by directly targeting LRP8 [129].

Esophageal cancer

The expression of LRP6 is increased in esophageal squamous cell carcinoma (ESCC). In addition, knockout of LRP6 inhibits migration, invasion and EMT of EC-109 and EC-9706 cells [130].lncRNA ESCCAL-1 is upregulated in ESCC for loss of methylation in its promoter [131]. It acts as a biomarker of poor prognosis, which exhibits promising diagnostic value [131–133]. ESCCAL-1 has been demonstrated to enhance the proliferation, migration, and invasion of ESCC cells while simultaneously inhibiting their apoptosis [134]. It also suppresses the ubiquitin-mediated degradation of Gal-1, thereby promoting the progression of the cell cycle [133]. The ablation of the ESCCAL-1 gene markedly curbs the in vivo growth of ESCC cells [131, 135]. ESCCAL-1 enhances the growth, migration, and invasion of ESCC by suppressing the miR-590/LRP6 pathway. Concurrently, LRP6, being a direct target of miR-590, intensifies the malignancy of cells via the activation of the Wnt/β-catenin signaling pathway in ESCC [136].

The roles of miRNA-regulated LRPs in breast cancer

Although LRP1 plays a role in inhibiting tumor development in many types of tumors, it may act as a different role in breast cancer (BC). The high expression of LRP1 could predict decreased overall survival [137]. LRP1 interacts with eHsp90α to regulate lymph angiogenesis by elevating the level of phosphorylated AKT [138]. eHsp90α-LRP1 complex activates EMT and migration in breast cancer cells through AKT, ERK and NF-κB pathway [139]. Outgrowth of lamellipodia protrusions is one of the characteristics of cancer cell migration and metastasis. LRP1 is capable of interacting with tPA to promote the formation of lamellipodia in breast cancer cells by triggering the NF-κB signaling pathway [140]. Acted as a receptor for secreted Hsp90α, LRP1 can inhibit hypoxia-induced apoptosis of breast cancer cells via ERK1/2 and the Akt pathways [141]. LRP1 facilitates tumor growth and the formation of new blood vessels, known as angiogenesis, in TNBC by modulating the TGF-β signaling pathway and the plasminogen/plasmin system [142]. LRP1 prompts migration and invasion of tumor cells in serum-free conditions by combined activating EGFR and the eHsp90α autocrine signaling [143].

It has been established that LRP6 is excessively expressed in BC [139]. Elevated levels of LRP6 expression are notably correlated with the status of HER-2 and Ki67. Patients with luminal B type BC who exhibit high LRP6 expression levels have significantly poorer survival rates compared to those with low LRP6 expression. LRP6 stimulates the formation of clones, invasion, and wound healing in MCF-7 and MCF-10 A cell lines. The suppression of LRP6 leads to the inhibition of xenograft growth [144]. Acting as a co-receptor for the Wnt/β-catenin pathway, LRP6 can enhance the progression of TNBC, as well as cell migration and invasion, by modulating the Wnt/β-catenin pathway [13].

miR-424 have been reported to be down-regulated in NSCLC, cervical cancer, ovarian cancer, prostate cancer and some digestive system tumor [145]. miR-424 regulates the cell cycle and cell proliferation probable by targeting CDK1, through the Hippo and ERK pathway [146]. The expression of miR-424 prompts invasion ability in extremely aggressive TNBC cell lines by direct targeting CDC42, thus inhibited tumorigenesis and metastasis in xenograft [147]. LRP6 is likely the most significant miR-424 target in the canonical wnt signaling. miR-424 exerted its function by reducing LRP6 mRNA levels and protein expression in BC cells [148]. In BC cell lines, the expression levels of miR-130a-3p are found to be reduced [149]. miR-130a-3p is also the target gene of several lncRNA. The expression of lncRNA HOTAIR was increased in BC. It associated with the metastasis in vitro and vivo and poor prognosis of patients through acting as a spong of endogenous miR-130a-3p [150]. Concurrently, the H19 hastens the proliferation, migration, and invasion of BC cells, and it also intensifies apoptosis through the miR-130a-3P/SATB1 pathway during the progression of BC [151]. Furthermore, miR-130a-3p hinders the proliferation, migration, and invasive capabilities of cells by specifically targeting the RAB5B gene [152]. Elevated levels of miR-130a-3p curb the proliferation, growth in the absence of attachment, and migratory behavior of TNBC cells by reducing the expression of WNT cascade genes, including LRP6 [149, 153]. Bioinformatic analysis suggests that LRP6 is likely a target gene for miR-130a-3p, which has the potential to repress the mRNA expression of LRP6 [153](Fig. 5).

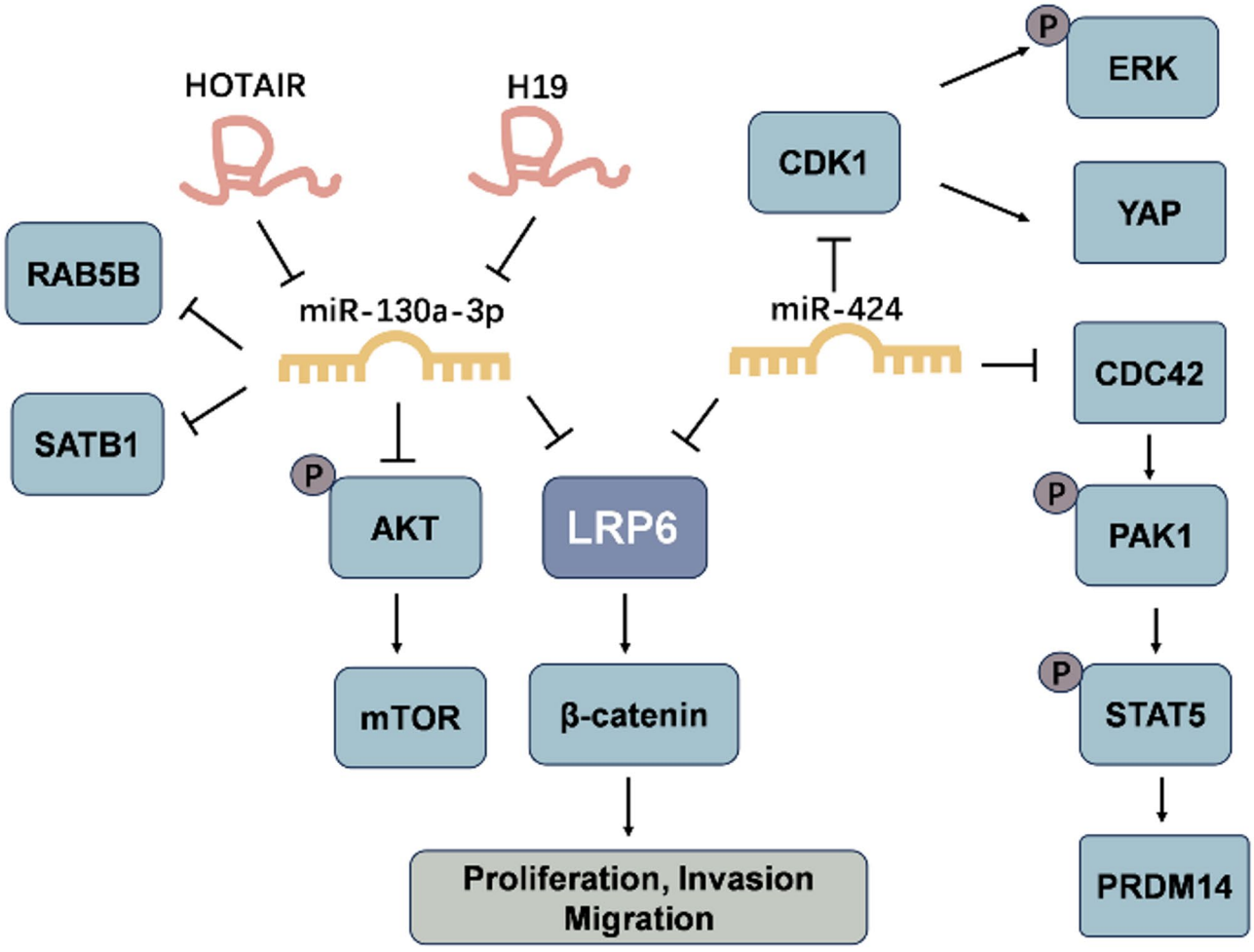

Fig. 5 The miRNA/LRPSs axis in breast cancer. miRNAs exert an inhibitory effect on the expression of LRP6, thereby impeding breast cancer progression. Conversely, lncRNAs can counteract the suppressive function of these miRNAs by downregulating their expression, leading to enhanced tumor proliferation, invasion, and migration in breast cancer

LRP8 is highly expressed in breast cancer, especially in ER−/HER2 + BC and TNBC [16, 154, 155]. Increased expression of LRP8 correlates with an unfavorable prognosis for BC patients [155]. LRP8 controlled cell survival, colony formation, cell cycle progression and tumorigenicity in a xenograft model in TNBC through canonical Wnt/β-catenin signaling pathway and MAPK pathways [16, 154]. Bioinformatics prediction and luciferase reporter assay confirms that miR-1262 is an upstream factor for LRP8 [155]. Previous studies find that overexpression of miR-1262 inhibited colon cancer [156], Gastric cardia adenocarcinoma (GCA) [157] and lung cancer [158]. miR-1262 diminishes the proliferative, clonogenic, invasive, and migratory abilities of BC cells, capabilities that are otherwise augmented by LRP8 [155].

The roles of miRNA-regulated LRPs in prostate cancer

Previous research indicated that LRP1B ranks among the top 10 genes most frequently absent in human cancer samples [159]. Meanwhile LRP1B is also one of the most recurrently mutated genes in prostate adenocarcinoma [160]. LRP1B mutations may have improved outcomes to ICI in many cancer types [161]. LRP1B can significantly inhibit growth and migration of colon cancer by interacted with DVL2 [162]. Diminished expression of LRP1B in renal cancer cells facilitates the processes of invasion, migration, and growth without the need for attachment [163]. miR-301b-3p exhibits increased levels in PC. A rise in miR-301b-3p expression correlates with a decrease in LRP1B mRNA levels within prostate cancer cells. miR-301b-3p is found to stimulate tumor progression, including growth, migration, and invasion, by directly suppressing LRP1B [164]. The expression of miR-500 is elevated in prostate cancer and is linked to

adverse clinical outcomes for patients with the disease. Knock-down of miR-500 inhibits PC growth [165] In PC tissues and cells, miR-500 is observed to be excessively expressed, while the expression of LRP1B is notably reduced. miR-500 is implicated in promoting cell proliferation and the cell cycle progression by specifically targeting LRP1B within PC cells [166].

miR-455-5p functions as a suppressor of tumorigenesis across a range of cancers, curtailing cellular proliferation, as well as the migration and invasion. In the context of PC, miR-455-5p serves as a tumor suppressor, hindering the proliferation of PC cells and inducing apoptosis by activating and cleaving caspase 3, as well as by targeting the CCR5 gene [167]. miR-455-5p is significantly under-expressed in PC, and its reduced levels are correlated with a less favorable prognosis for patients with the disease. miR-455-5p impedes the migration and invasiveness of prostate cancer cells. The increased expression of miR-455-5p is known to repress the expression of LRP8, which has been confirmed as a target gene for miR-455-5p using the TargetScan Human 7.1 database. High levels of LRP8 expression correlate with a negative outcome for patients with prostate cancer [168].

The roles of miRNA-regulated LRPs in thyroid carcinoma

CpG island methylation and DNA copy number loss often occurs in LRP1B in thyroid carcinoma (TC). LRP1B functions to suppress tumorigenesis by curbing the growth and invasion of TC cells [169–171]. LRP1B expression is down-regulated in TC cells [172]. miR-548a-5p was overexpressed in cancer cell lines, and prompts tumor growth, cell invasion and MMP-2 reduction by targeting LRP1B in vitro and in vivo [173]. miR-196a-5p is up-regulated in TC tissue and showed an oncogenic role in TC cells [174]. It enhances the proliferation, migration, and invasion of TC cells through direct binding to the 3'UTR of the LRP1B gene [172] (Fig. 6A).

It has been documented that LRP4 is excessively expressed in PTC. The SNPs within the LRP4 gene significantly influence an individual's genetic predisposition to PTC [175]. LRP4 influences the proliferation, migration, invasion, and EMT of cells through the activation of the PI3K/AKT pathway [5]. miR-199a-5p impedes tumor migration, invasion, and EMT in living organisms by reducing the expression of SNAI1 [176]. miR-199a-5p curbs cell migration and invasion through the down-regulation of PD-L1 and Claudin-1 [177]. miR-199a-5p diminishes the viability of TC cells by reducing the proportion of cells in the G2/M and S phases [178]. LRP4 may be the target gene of miR-199a-5p predicted by the miRWalk database (version 2.0) [179] miR-429 exhibits reduced expression in TC tissues and cell lines. It inhibits the proliferation, migration, and invasion of cells, and also induces apoptosis in the TC cell line [180]. In thyroid carcinoma, miR-429 is the target gene of multiple lncRNAs. OIP5-AS1 enhances the proliferation, metastasis and inhibited the apoptosis via adsorbing miR-429 [181]. miR-429 is the target of RNF185-AS1. RNF185-AS1 enhances tumor growth both by sequestering miR-429, thereby facilitating the expression of LRP4 [182] (Fig. 6B).

LRP6 exert as highly tumor-promoting function by activating Wnt/β-catenin pathway in PTC [183]. miR-146b-5p is over expression and shows correlation with the clinicopathological status of PTC. miR-146b-5p stimulates cell proliferation, migration, invasion, and cell cycle advancement in vitro by directly binding to the CCDC6 [184]. The Wnt/β-catenin signaling pathway is pivotal in the progression of TC [185]. Different from other miRNA that targeted LRP6, miR-146b-5p played a role in promoting LRP6 expression. miR-146b-5p increases the LRP6 through directly targeted ZNRF3, which leading to the ubiquitination and degradation of LRP6 [183]. miR-1271 is under-expressed in PTC, where it impedes cell migration, invasion, proliferation, and EMT by targeting IRS1 and inhibiting the AKT pathway [186]. LRP6 has been identified as a direct target of miR-1271. In PTC, the upregulation of Circ_0011373 sequesters miR-1271, leading to increased expression of LRP6. This mechanism may potentially influence the cell cycle, migration, invasion, and apoptosis of PTC cells [187] (Fig. 6C).

The roles of miRNA-regulated LRPs in reproductive system cancers

The NCBI database indicates that LRP6 is abundantly expressed in placental tissues, yet it shows low expression in trophoblast cell lines when compared to JEG-3 gestational choriocarcinoma cells. The overexpression of LRP6 is found to enhance the proliferation and migration of trophoblast cells by upregulating the expression of MMP-2 and MMP-9, while also reducing the levels of tissue inhibitors of TIMP-1 and TIMP- 2. Conversely, miR-346 is more highly expressed in trophoblast cell lines than in JEG-3 gestational choriocarcinoma cells. Elevated levels of miR-346 are observed to suppress the proliferation of these cells and decrease their migration and invasion rates by directly targeting LRP6 in both JEG-3 and gestational choriocarcinoma cells [188].

An excess of LRP8 notably boosts the proliferation, migration, and invasive capabilities of ovarian cancer cells. There is an inverse relationship exists between the expression levels of miR-362-3p and LRP8 in ovarian cancer. miR-362-3p hinders the proliferation, migration, and invasion of ovarian cancer cells by directly targeting LRP8, which results in the downregulation of MMP-2, MMP-9, as well as integrins α5 and β1 [189]. Multiple

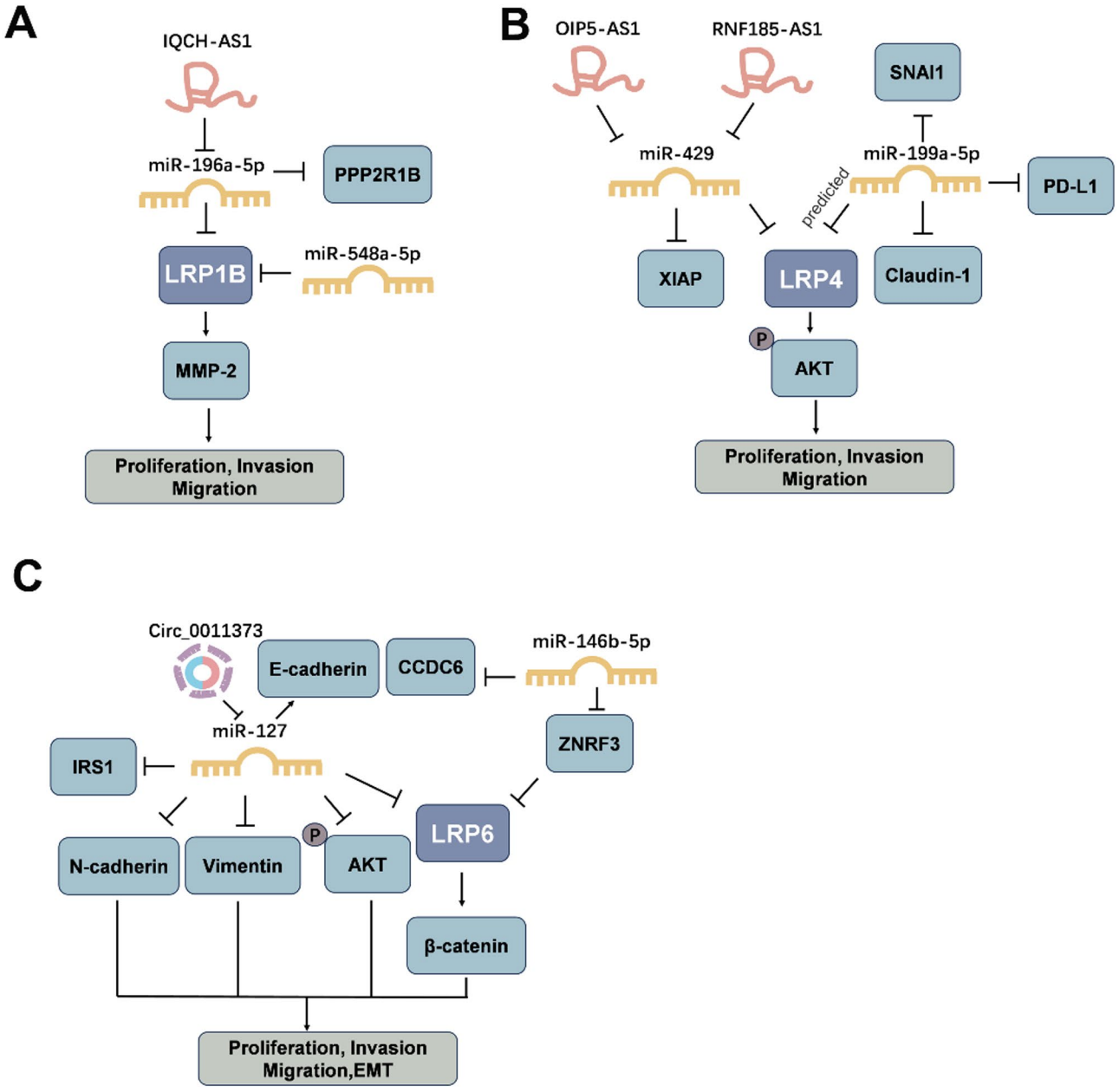

Fig. 6 The miRNA/LRPSs axis in thyroid carcinoma. (**A**) IQCH-AS1 upregulates the expression of LRP1B by suppressing miR-196a-5p, consequently promoting proliferation, invasion, and migration in thyroid carcinoma. (**B**) LncRNAs stimulate the expression of LRP4 by inhibiting miR-429, thereby enhancing tumor proliferation, invasion, and migration in thyroid carcinoma (**C**) In hepatocellular carcinoma, miRNAs have been identified to negatively regulate LRP6. Furthermore, the circRNA Circ_0011373 can inhibit miR-127, leading to increased LRP6 expression and promoting cell proliferation, invasion, migration, and EMT

investigations have uncovered miR-362-3p's regulatory influence in ovarian cancer, showing that it is underexpressed in both epithelial ovarian cancer tissues and cell lines. It suppresses cell proliferation and migration through the downregulation of MyD88 expression [190]. miR-362-3p also impedes the growth and advancement of ovarian cancer by directly interacting with its target gene SERBP1 in vivo [191]. Intriguingly, MALAT1 could prompt proliferation, invasion, and SU chemoresistance, but inhibits apoptosis through interact with miR-362-3p in RCC [192]. Reducing the levels of MALAT1 can curb the proliferation and diminish the invasive and migratory capacities in HCC by targeting miR-362-3p [193]. MALAT1 could also bind miR-195 to up-regulate LRP6 expression in CRC [55]. Based on the above conclusions, miR-362-3p may perform as a regulator of LRP6 in ovarian tumors, but no relevant research has been found so far.

The roles of miRNA-regulated LRPs in melanoma

LRP1 level is highly elevated in melanoma tissues. LRP1 is indispensable in YAP-induced melanoma tumorigenesis in vitro and in vivo [194]. LRP1 plays a crucial role in PAI-1-induced FAK phosphorylation and the invasive behavior of macrophages in melanoma [195]. Moreover, LRP1 enhances melanoma cell proliferation and massive lung metastasis by activating ERK and MMP-9. It is also critical for drug resistance [196]. APOE2/LRP1 axis may play important roles in tumor growth, metastasis, and protein synthesis in melanoma [197].

miR-103 and miR-107 are miRNAs related to each other, with a difference of just one base in their 3' regions [198]. They have different functions in different tissues. Research has shown that the miR-103/107 cluster promotes the mobility of CRC cells by directly targeting metastasis suppressors, including death-associated protein kinase DAPK and KLF4 [36], triggers a prolonged duration of Wnt/β-catenin signaling by targeting Axin2 [37]. miR-103/107 modulates cell proliferation via the PI3K/AKT signaling pathway, in part by directing its action towards the PTEN [199]. Additional research has assessed that miR-103/107 diminishes the functionality of P-gp thereby increasing the sensitivity of GC cells to the chemotherapeutic agent DOX by targeting Cav-1 [200]. In melanoma, miR-107 is significantly downregulated, miR-107 can reduce cell proliferation, migration and invasion by targeting POU3F2 in melanoma [201]. Moreover, LINC00662 facilitates the advancement of melanoma by engaging the miR-107/POU3F2 regulatory axis and stimulating the β-catenin pathway [202]. miR-103/107 reduces cell proliferation and induced cell apoptosis by targeting LRP1 [203]. The function of LRP1 in different melanoma cells may also be different. A study found miR-199a-3p, miR-199a-5p, and miR-1908 which predicted metastasis-free survival in melanoma promote metastasis, invasion, and angiogenesis of melanoma by targeting APOE3 and suppressing LRP1 signaling [204] (Fig. 7).

The roles of miRNA-regulated LRPs in glioblastoma

The expression of LRP1 is increased under hypoxia, it facilitates glioblastoma (GBM) motility and invasion in an AKT dependent manner [205]. LRP1 is expressed on mast cells (MCs) and is critical for migration of MCs induced by PAI-1 [206]. LRP1 is strongly expressed in the angiogenic part of the tumor, and glioblastoma cells. It acts as a regulator of CXCR3, which prompts tumor cell invasion [207]. LRP1 facilitates drug delivery system such as Au-DOX@PO-ANG due to its capacity to penetrate the blood-brain barrier and access the central nervous system [208]. The expression of LRP-1 is significantly higher in GBM, LRP-1 prompts cell survival, proliferative migration, and decreases apoptosis [209]. In GBM cell line, LRP1 and miR-124-3p could be identified as hypoxia biomarkers [210]. Whether LRP1 is regulated by miR-124 have not been reported. Recent studies have found that miR-124, miR-128 may inhibit the expression of LRP1 by targeting ELF4 [211].

miRNA-205 is markedly under-expressed in glioma, functioning as a suppressor of tumor growth by specifically targeting VEGF-A [212, 213]. The serum concentration of miR-205 is independently linked to overall survival rates and is identified as an individual diagnostic marker [214]. miR-205 inhibits cell migration, invasion and prevented EMT through inhibiting of the Akt/mTOR signaling pathway in GBM [215]. miR-205 is crucial in counteracting the self-renewal of glioma stem cells (GSCs) and their resistance to irradiation [212]. The 3'UTR of the LRP1 gene can be targeted by miR-205, which suppresses cell migration and invasion through the reduction of LRP1 expression [216](Fig. 8A).

LRP6 is highly expressed in gliomas, the expression of LRP6 links with overall survival in all glioblastoma [217, 218]. Elevated levels of LRP6 expression are recognized for initiating Wnt pathway activation, promoting cell proliferation, and contributing to the development of tumors in glioblastoma cells [219]. The expression of miR-513c is found to be reduced in tissues and cell lines of GBM. miR-513c suppresses the proliferation of GBM cells by directly targeting the 3'UTR of the LRP6 gene [220]. Additionally, miR-513c-5p facilitates the suppression of neuroblastoma cell proliferation, colony formation, and invasive capabilities by modulating the silencing of DLX6-AS1, it also causes cell cycle arrest and apoptosis through the PLK4 pathway in vitro [221]. LOC728196 acts as a molecular sponge to miR-513c, which in turn facilitates the growth, migration, and invasiveness of glioma cells by modulating the expression of TCF7 [222].

miR-137 exhibits reduced expression levels in glioblastoma, and its diminished levels correlate with an unfavorable prognostic profile for individuals afflicted with GBM [223]. miR-137 deduces GBM cell proliferation, invasion and angiogenesis by targeting a series of genes, including EZH2, Cox-2, CXCL12, SP1 and CSE1L [224–228]. miR-137 curbs the proliferation of glioblastoma and leads to G1 phase cell cycle arrest in glioblastoma multiforme cells [229]. miR-137 inhibits proliferation, migration and invasion of glioblastoma through Akt/mTOR signaling by targeting PTP4A3 [230]. miR-137 enhances cell growth and reduces cell apoptosis by targeting the 3'-UTR of the EGFR [231]. The downregulation of HOTAIRM1 expression impeded the proliferation and invasive capabilities of glioblastoma cells by serving as a sponge to miR-137 [227]. lncRNA HAS2-AS1 promotes proliferation of GBM cell and tumorigenesis of nude mouse by downregulating of miR-137 [232]. miR-137 sensitized GBM cells to the TRAIL-mediated apoptosis by targeting XIAP

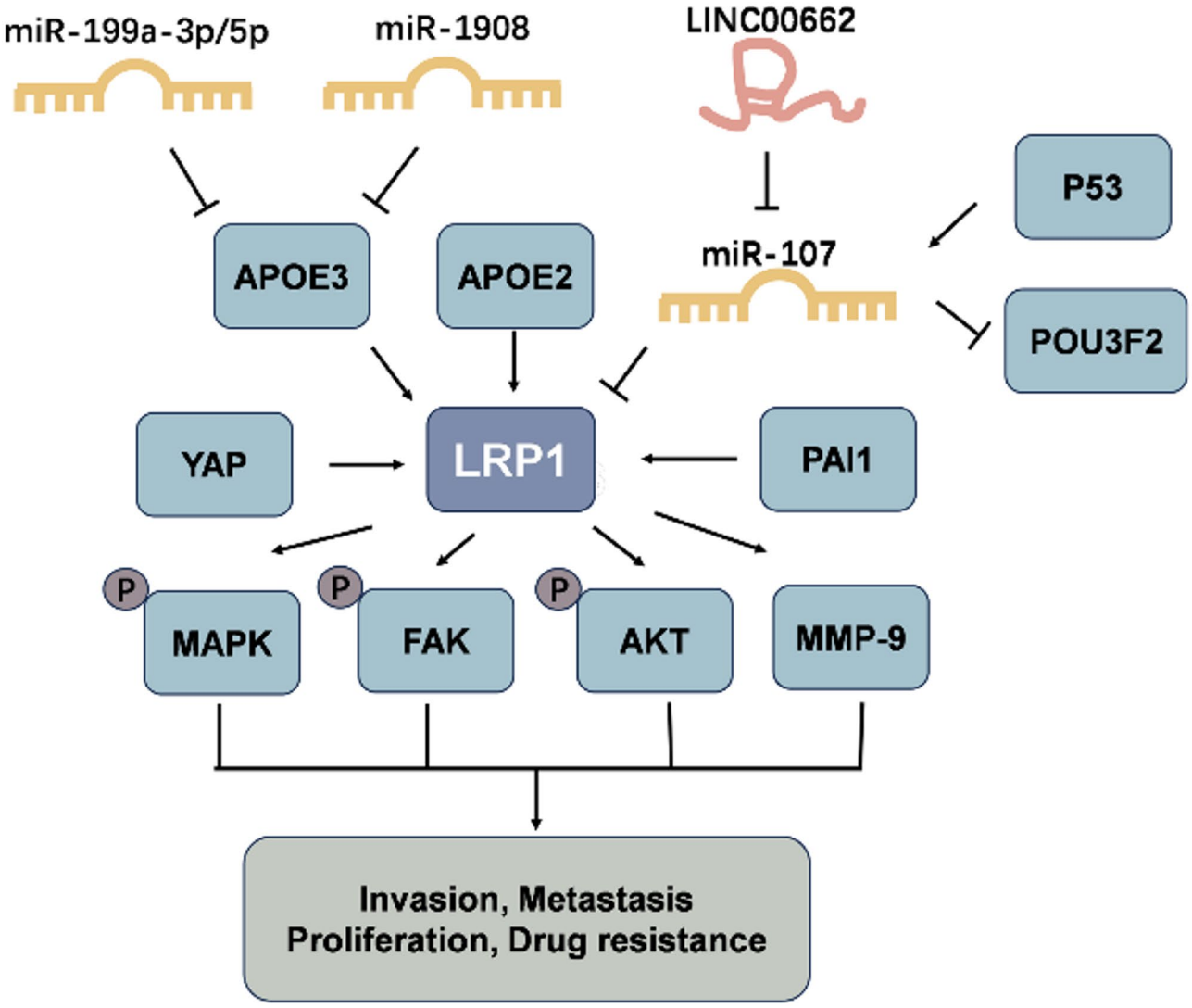

Fig. 7 The miRNA/LRPSs axis in melanoma. LINC00662 promotes the expression of LRP1 by suppressing miR-107, which in turn enhances proliferation, invasion, metastasis, and drug resistance in melanoma

[233]. LRP6 is a target gene of miR-137, which can suppress invasion, EMT and enhance the chemosensitivity of GBM cells to TMZ by reducing LRP6 expression, subsequently affecting β-catenin and its downstream signaling pathways [218].

LINC01094 exhibits elevated expression levels in tissues and cell lines of GBM [234, 235]. LINC01094 facilitates the proliferation, migration, and invasion of cells, and suppresses apoptosis by acting as a sponge for miR-126-5p [235] and miR-577 [234] in GBM. miR-577 is found to be under-expressed in GBM tumor samples and cell lines, where it inhibits GBM growth by directly targeting LRP6 and β-catenin [236]. miR-126 have been reported to regulate the expression of LRP6 in many tumors and non-tumor diseases [115, 237–241]. Whether LINC01094 can regulate LRP6 through miR-126 and miR-577 in GBM needs further study.

ADAMTS9AS1 is upregulated in GBM tissues and cell lines. ADAMTS9-AS1 influences the proliferation, apoptosis, migration, and stem-like properties of glioma cells [187]. ADAMTS9-AS1 may have a complex regulatory effect on LRP family members. In GBM, ADAMTS9-AS1 is capable of interacting with miR-128 and miR-150, leading to the upregulation of the RAS/MAPK signaling pathway, as well as the LRP6 and Wnt pathways [242]. In breast cancer, ADAMTS9-AS1 can activate the JAK/STAT signaling by binding miR-301b-3p [243]. miR-301b-3p could potentially enhance the proliferation, migration, and invasiveness of PC cells by targeting LRP1B [164]. For ADAMTS9-AS1 is under-expressed in PC and may serve as a prognostic indicator for the overall survival of PC patients. It is believed that ADAMTS9-AS1 could exert its tumor-suppressive role by modulating LRP1B in prostate cancer (Fig. 8B).

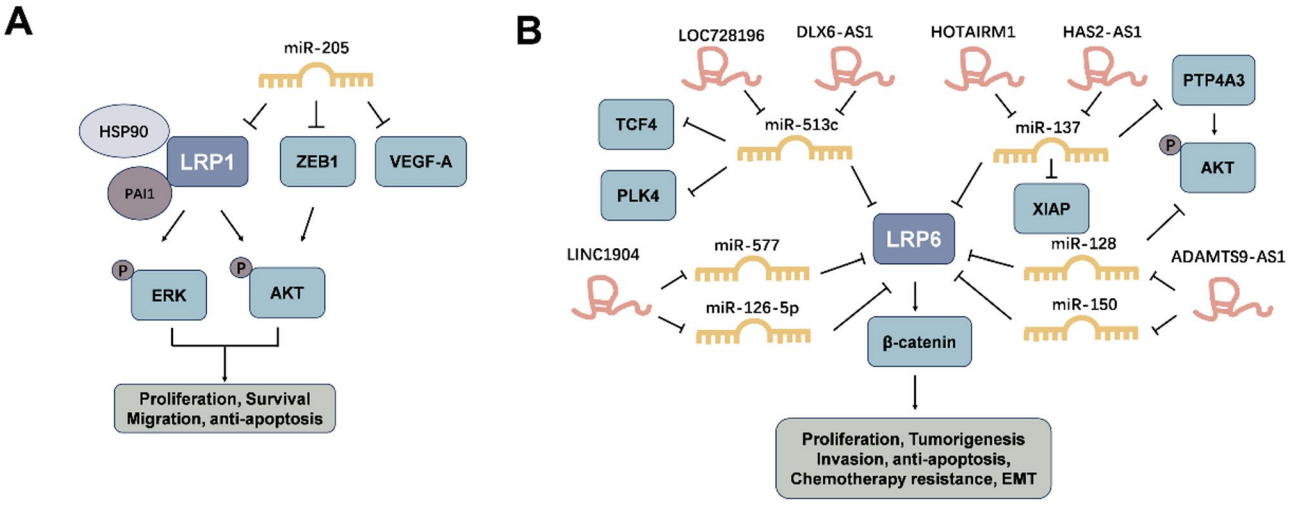

Fig. 8 The miRNA/LRPSs axis in glioblastoma. reduce apoptosis in glioblastoma. (**A**) miR-429 inhibits the expression of LRP1, which can induce proliferation, migration, and survival of glioblastoma cells, while reducing apoptosis. (**B**) Tumor suppressor miRNAs in glioblastoma exert their inhibitory function on cancer progression by inhibiting LRP6. Oncogenic lncRNAs, on the other hand, augment LRP6 expression by suppressing these miRNAs, thereby inducing cell proliferation, tumorigenesis, EMT, invasion, and chemotherapy resistance, and reducing apoptosis in glioblastoma

The roles of miRNA-regulated LRPs in lung cancer

A study indicates that LRP5 is under-expressed in six out of seventeen cases of lung squamous cell carcinoma [244]. The LRP5 rs3736228 and rs64843 SNPs have been notably linked to an elevated risk for NSCLC and squamous cell carcinoma (SCC), respectively [245]. There was a robust inverse relationship between miR-375 expression levels and LRP5 in both Adenocarcinoma (AC) and Small Cell Lung Cancer (SCLC). Previous research has demonstrated that miR-375-3p inhibits osteogenesis by targeting the LRP5 gene in MC3T3-E1 cells [246]. In H82 cells, the luciferase activity of the reporter for the putative target sites within the 3'UTR of the LRP5 mRNA was not significantly reduced by miR-375, and the ectopic expression of miR-375 had minimal impact on the suppression of the LRP5 protein. It suggests that miR-375 may regulate LRP5 through indirect pathways [247]. Therefore, more experimental results are needed to confirm the regulatory mechanism of miR-375 on LRP5 in lung cancer.

The earliest research found that overexpression of LRP8 is observed in 11 of the 13 lung cancer samples. This result suggests that LRP8 may play an oncogenic role in lung cancer [248]. Previous studies have indicated that LRP8 correlates with adverse clinicopathological features and the prognosis of patients with NSCLC. LRP8 has been shown to enhance the proliferation of NSCLC cells both in vitro and in vivo, and it plays a role in the progression and metastasis of NSCLC by modulating the Wnt/β-catenin signaling pathway [15]. miR-30b-5p is significantly correlated with the overall survival rate of lung cancer, which can be utilized to develop a risk scoring model serving as a prognostic signature for lung cancer [249]. miR-30b-5p exhibits low expression in A549/DDP cells and enhances their sensitivity to DDP. It targets LRP8 in lung cancer, and the increased sensitivity of A549 cells to DDP induced by miR-30b-5p can be negated by the overexpression of LRP8 [250].

The roles of miRNA-regulated LRPs in other type of cancers

The expression LRP1 is strong in dermatofibrosarcoma protuberans (DFSP), but weak in dermatofibroma (DF), but is not seen in normal fibroblasts [251]. Previous research find miR-205 as the most differentially expressed miRNA on cutaneous squamous cell carcinoma (cSCC) and malignant skin cancer [252]. miR-205 prompts cell cycle arrest at the G2M phase in melanoma cell line [253] and suppressed the migration, invasion and proliferation of cancer cell [254]. LRP1 is a target of miR-205. In DFSP, the downregulation of miR-205 results in aberrant cell proliferation, which losing the ability to inhibit the expression of LRP1 and triggers the ERK pathway [251]. miR-196a directly targets LRP4 in neuroendocrine tumor cell lines CNDT2.5 and NCI-H727, and it modulates downstream genes associated with the WNT signaling pathway, including LRP5 and LRP6 [255].

Conclusion and remarks

In recent years, a multitude of scientific experiments have played a significant role in exploring new molecular mechanisms of tumors, developing new tumor treatment strategies, and researching new anti-tumor drugs. Studying the molecular pathways of tumors is of great significance for a deeper understanding of the biological characteristics and development mechanisms of tumors,

Table 1 The regulatory roles of MiRNA in various human malignancies

Cancer Type	miRNA	Signaling Pathways/Targeting Gene	References
Colorectal cancer	miR-103	LRP1, p53, HIF-1.	[29–30]
	miR-107	LRP1, PRE3/4.	[31–33]
	miR-92a	LRP6, DKK3.	[49]
	miR-15	LRP6, RUNX2.	[55]
	miR-487b	LRP6, MYC, SYZ12, KRAS.	[58]
Pancreatic cancer	miR-429	LRP1, TBK1, FOXD1, ERK.	[63–64, 66–67]
	miR-26b	LRP6, CDK14	[73]
	miR-194	LRP6	[74]
	miR-15a-5p	BHLHE40	[81]
	miR-577	LRP6, PI3K/AKT, LIN28B, COL1A1	[82–84]
	miR-454	LRP6	[89]
Hepatocellular cancer	miR-455-5p	IGF-1R, AKT, GLUT1, PD-L1, LRP4	[95–97]
	miR-1269a	LRP6	[105]
	miR-202	HK2, BCL2, LRP6	[106–108]
	miR-432	WNT/β-catenin signaling, LRP6.	[109]
	miR-610	-catenin, LRP6,	[110]
	miRNA-126-3p	LRP6, WNT/β-catenin signaling	[114]
	miR-26a/b-5p	LRP6, WNT/β-catenin signaling	[116]
	miR-338	LRP6	[118]
Gastric cancer	miR-140-5p	LRP4, WNT/β-catenin signaling, YES1, NDRG3	[6, 119, 121]
	miR-545-3p	EMS1, LRP5	[125, 126]
	miR-142	LRP8, ERK	[20]
Esophageal Cancer	miR-590	LRP6, WNT/β-catenin signaling	[136]
breast cancer	miR-424	CDK1, CDC42, LRP6	[146–148]
	miR-130a-3p	SATB1, RAB5B, AKT/mTOR signaling, LRP6	[151–153]
	miR-1262	WNT/β-catenin signaling, MAPK, LRP8	[16, 154–155]
Prostate cancer	miR-301b-3p	LRP1B	[164]
	miR-500	LRP1B	[166]
	miR-455-5p	Caspase-3, CCR5, LRP8	[167–168]
Thyroid carcinoma	miR-196a-5p	LRP1B, PPP2R1B	[172, 174]
	miR-548a-5p	MMP-2, LRP1B	[173]
	miR-199a-5p	SNAI1, PD-L1, Claudin-1	[176–177]
	miR-429,	XIAP, LRP4	[181–182]
	miR-146b-5p	LRP6, ZNRF3, CCDC6, WNT/β-catenin signaling	[183–185]
	miR-1271	IRS, AKT, LRP6, WNT/β-catenin signaling	[186–187]
Reproductive system cancers	miR-346	LRP6	[188]
	miR-362-3p	MMP-2, MMP-9, integrins α5, integrins β1 SERBP1	[189–191]
Melanoma	miR-103/107	DAPK, KLF4, Axin2, AKT, PTEN Cav-1, POU3F2, β-catenin, LRP1	[36, 37, 199–203]
	miR-199a-3p/5p, miR-1908	APOE3, LRP1	[204]
Glioblastoma	miR-124	ELF4, LRP1	[211]
	miRNA-205	VEGF-A, AKT/mTOR signaling, LRP1	[212–216]
	miR-513c	LRP6, PLK4, TCF7	[220–222]
	miR-137	LRP6, EZH2, Cox-2, CXCL12, SP1, CSE1L, PTP4A3, XIAP	[218, 224–228, 230, 233]
	miR-577	LRP6, WNT/β-catenin signaling	[236]
	miR-128, miR-150, miR-577, miR-126	RAS/MAPK signaling, LRP6, WNT/β-catenin signaling	[115, 236–242]
Lung cancer	miR-375	LRP5	[246]
	miR-30b-5p	LRP8	[250]
Dermatofibrosarcoma protuberans	miR-205	LRP1, ERK	[251]
Neuroendocrine tumor	miR-196a	LRP4, LRP5, LRP6	[255]

as well as for guiding clinical treatment. The LRPs family, a group of transmembrane proteins, is crucial for cellular signal transduction and participates in a multitude of biological processes. A growing body of research indicates that the LRPs family is instrumental in tumor biology, with functions ranging from the facilitation or suppression of tumor cell proliferation, migration, and survival to the modulation of the tumor microenvironment. LRPs are involved in the regulation of many key oncogenes, and they also act as target genes for a range of microRNAs. Here, we have elaborated the role of miRNA in regulating LRP and its downstream genes in the pathogenesis of various human malignancies (Table 1). Progress in miRNA/LRP research in human oncology holds the promise of elucidating the intricate molecular controls of cancer, potentially pointing the way for novel avenues in cancer management and therapeutics.

Abbreviations

3′	UTR 3′untranslated region
5-FU	5-fluorouracil
A549/DDP	A cisplatin drug resistant cell line
ABCG1	ATP-binding cassette transporter G1
AC	Adenocarcinoma
ADAMTS9AS1	ADAMTS9 Antisense RNA 1
AKT	Protein kinase B
APOE	Lipid transporter apolipoprotein E
Axin2	Axis Inhibition Protein 2
BC	Breast cancer
BCL2	B-cell lymphoma/leukemia type 2
BHLHE40	Basic helix-loop-helix domain containing, class b, 2
Cav-1	Caveolin-1
CCDC6	Coiled-coil domain containing 6
CDC42	Cell division control 42
CDK1	Cyclindependent kinase 1
CDK14	Cyclin-dependent kinase 14
ceRNA	Endogenous RNA
circFBLIM1	CircRNA filamin binding LIM protein 1
Cox-2	Cyclooxygenase-2
CRC	Colorectal cancer
cSCC	Cutaneous squamous cell carcinoma
CSE1L	CSE1 chromosome segregation 1-like
CXCL12	C-X-C motif ligand 12
CXCL12	CXC chemokine ligand 12
CXCR3	CXC chemokine receptor 3
CXCR4	CXC chemokine receptor 4
DAPK	Death-associated protein kinase
DF	Dermatofibroma
DFSP	Dermatofibrosarcoma protuberans
DKK3	Dickkopf-3
DLGAP1-AS1	Discs large associated protein 1 antisense RNA 1
DLX6-AS1	Distal-less homeobox 6 antisense RNA 1
Dox	Doxorubicin
DVL2	Dishevelled segment polarity protein
E2F6	E2F transcription factor 6
EGFR	Epidermal growth factor receptor
eHsp90	Hsp90 protein
eHSP90α	Extracellular heat shock protein-90α
ELF4	E74-like factor 4
EMS1	Eleven-Nineteen Lysine-Rich Carcinoma-Related Gene 1
EMT	Epithelial-to-mesenchymal
EOF	Epirubicin, Oxaliplatin, and 5-Fluorouracil
ERK1/2	Extracellular signal-regulated kinase1/2
ESCC	Esophageal squamous cell carcinoma
ESCCAL-1	Esophageal squamous cell carcinoma-associated lncRNA-1
EZH2	Enhancer of zeste homolog 2
FAK	Focal adhesion kinase
FGD5-AS1	FYVE, RhoGEF, and PH domain containing 5 antisense RNA 1
FRMD5	FERM domain containing 5
FZD	Frizzled
Gal-1	Galectin-1
GBM	Glioblastoma
GC	Gastric cancer
GLUT1	Glucose transporter type 1
GSC	Glioma stem cells
HAS2-AS1	Hyaluronan Snthase 2 Antisense RNA 1
HCC	Hepatocellular carcinoma
HER-2	Human Epidermal Growth Factor Receptor 2
HIF-1	Hypoxia-inducible factor-1
HOTAIR	LncRNA HOX transcript antisense intergenic RNA
HOXA-AS3	HOXA cluster antisense RNA 3"
HUMT	Human Mitochondrial Translation
ICI	Immune checkpoint inhibitors
IGF-1R	Insulin-like growth factor 1 receptor
IQCH-AS1	IQCH antisense RNA 1
IRS1	Insulin receptor substrate 1
JAK	Janus kinase
KLF4	Krüppel-like factor 4
KRAS	Kirsten ras oncogene
LINC01094	Long intergenic non-protein coding RNA 1094
LncRNA	Long non-coding RNA
LOC728196	MIR34B and MIR34C host gene
LRPs	Low-density lipoprotein receptor-related protein
MALAT1	Metastasis associated with lung adenocarcinoma transcript 1
MAPK	Mitogen-activated protein kinase
MCs	Mast cells
MIF	Macrophage migration inhibitory factor
miRNAs	MicroRNAs
MMP-2	Matrix metalloproteinase 2
MMP-9	Matrix metalloproteinase 9
MPA	Mycophenolic acid
mRNA	Messenger RNA
mTORC1	Mechanistic target of rapamycin complex 1
MyD88	Myeloid differentiation factor88
NCBI	National Center for Biotechnology Information
NDRG3	N-myc downstream-regulated gene 3
NF-κB	Nuclear factor-kappa B
NSCLC	Non-Small Cell Lung Cancer
NT-3	Neurotrophin-3
OIP5-AS1	Opa Interacting Protein 5 Antisense RNA 1
OS	Overall survival
PAI-1	Plasminogen activator inhibitor-1
pak1	P-21-activated kinase 1
PC	Prostate cancer
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed Death-Ligand 1p
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PLK4	Polo-like kinase 4
POU3F2	POU Class 3 Homeobox 2"
PPP2R1B	Protein phosphatase 2
prdm14	PR-domain containing 14
PRE3/4	Proteasome subunit pre3/4
PTC	Papillary thyroid cancer
PTEN	Phosphatase and tensin homologue deleted on chromosome ten
PTP4A3	Protein tyrosine phosphatases (PTP) 4A3
RAB5B	Ras-related protein Rab-5B
RAS	Renin-Angiotensin System
RCC	Renal cell carcinoma
RNF185-AS1	RNF185 Antisense RNA 1
RUNX2	Runt-related transcription factor 2
SATB1	Special AT-rich sequence-binding protein-1
SBF2-AS1	SET-binding factor 2 antisense RNA1
SCC	Squamous cell carcinoma
SCLC	Small Cell Lung Cancer

SERBP1	Serum amyloid a binding protein 1
SNAI1	Snail family zinc finger 1
SNHG20	Small nucleolar RNA host gene 20
SNPs	Single nucleotide polymorphisms
SP1	Specificity Protein 1
STAT	Signal transducer and activator of transcription
SU	Sunitinib
SUZ12	Suppressor of Zeste 12
TC	Thyroid carcinoma
TCF7	Transcript tion factor 7
TIMP-1	Tissue inhibitor of metalloproteinase-1
TIMP-2	Tissue inhibitor of metalloproteinase-2
TMPO-AS1	Thymopoietin associated lncRNA 1
TMZ	Temozolomide
TNBC	Triple-negative breast cancer
TNM	Tumor-node-metastasis
tPA	Tissue plasminogen activator
VEGF-A	Vascular endothelial growth factor A
WNT	Wingless-Type MMTV Integration Site Family
XIAP	X-linked inhibitors of apoptosis protein
YAP	Yes-associated protein
YES1	Yamaguchi sarcoma viral oncogene homolog 1
ZNRF3	Zinc RING finger 3

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