REVIEW

Dysfunction and ceRNA network of the tumor suppressor miR-637 in cancer development and prognosis

Jinze Shen, Chenhao Liang, Xinming Su, Qurui Wang, Yufei Ke, Jie Fang, Dayong Zhang* and Shiwei Duan*

Abstract

MicroRNAs (miRNAs) are a class of small non-coding RNAs ranging from 17 to 25 nt in length. miR-637 is down-regulated in most cancers and up-regulated only in clear cell renal cell carcinoma (ccRCC). miR-637 can target 21 protein-coding genes, which are involved in the regulation of cell growth, cell cycle, cell proliferation, epithelial-mesenchymal transition (EMT), cancer cell invasion and metastasis, etc. In glioma, the transcription factor ZEB2 can bind to the miR-637 promoter region and inhibit miR-637 expression. Besides, miR-637 could be negatively regulated by competing endogenous RNA (ceRNAs) comprising 13 circular RNA (circRNAs) and 9 long non-coding RNA (lncRNAs). miR-637 is involved in regulating five signaling pathways, including the Jak/STAT3, Wnt/β-catenin, PI3K/AKT, and ERK signaling pathways. Low miR-637 expression was significantly associated with larger tumors and later tumor node metastasis (TNM) staging in cancer patients. Low miR-637 expression was also associated with poorer overall survival (OS) in cancer patients such as glioblastoma and low-grade gliomas (GBM/LGG), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), and ovarian cancer (OV). Low expression of miR-637 increases the resistance of colorectal cancer (CRC) and human cholangiocarcinoma (CHOL) cancer cells to three anticancer chemotherapeutics (gemcitabine (dFdC), cisplatin (DDP), and oxaliplatin (OXA)). Our work summarizes the abnormal expression of miR-637 in various cancers, expresses on the ceRNA regulatory network and signaling pathway involved in miR-637, and summarizes the effect of its abnormal expression on the biological behavior of tumor cells. At the same time, the relationship between the expression levels of miR-637 and its related molecules and the prognosis and pathological characteristics of patients was further summarized. Finally, our work points out the insufficiency of miR-637 in current studies and is expected to provide potential clues for future miR-637-related studies.

Keywords: miR-637, Cancer, ceRNA, Dysregulation, Prognosis, Drug resistance

Facts

1. The expression of miR-637 is down-regulated in almost all cancers, And the expression of miR-637 is only up-regulated in ccRCC
2. miR-637 exerts tumor suppressor effect in cancer through ceRNA network.
3. Low expression of miR-637 is closely related to the poor prognosis of cancer.

Open questions

1. Additional ceRNA networks for miR-637 in cancer need to be discovered.
2. What is the relationship between miR-637 and resistance to other anticancer drugs?
3. What is the link between the expression of miR-637 and its host gene DAPK3?
4. Why is the abnormal expression pattern and role of miR-637 different in ccRCC than in other cancers?

Introduction
MicroRNA (miRNA) is a small single-stranded non-coding RNA (ncRNA) with a length of 17~25nt. It can usually bind to the 3'-untranslated region (3'-UTR) of messenger RNA (mRNA) and affect the mRNA stability or protein translation process, thereby down-regulating messenger RNA (mRNA) and affect the mRNA stability usually bind to the 3'-untranslated region (3'-UTR) of.

miR-637 is located in the fifth intron of death associated protein kinase 3 (DAPK3) in the 19p13.3 region. DAPK3 belongs to the superfamily of calcium-dependent serine/threonine kinases and can regulate apoptosis and autophagy in various tumors. miR-637 is under-expressed in most cancers. miR-637 can directly target 21 protein-coding genes, thereby regulating cell cycle, growth, proliferation, epithelial-mesenchymal transition (EMT), cancer cell invasion and metastasis, and other cell behaviors. miR-637 is competitively bound by ceRNA in cancer, and the low expression of miR-637 promotes the occurrence and development of cancer. The target genes of miR-637 are involved in various signaling pathways, which in turn affect the progression of cancer. miR-637 can increase the sensitivity of colorectal cancer (CRC) cancer cells to drugs such as gemcitabine (dFdC), gemcitabine (DDP), and oxaliplatin (OXA).

Although miR-637 has been extensively studied in cancer, there is currently no systematic review of miR-637. Our work provides an overview of the aberrant expression of miR-637 in cancer and summarizes the role of miR-637 in acting as a tumor marker and inhibiting tumor progression.

miR-637 and its host gene DAPK3
Death-associated protein kinases are a family of five Ser/Thr kinases with conserved catalytic domains that are closely related to cell death. DAPK3 regulates programmed cell death, including apoptosis and autophagy. miR-637 is located in 19p13.3, the fifth intron of DAPK3. Since there is no study on the correlation between DAPK3 and miR-637, we have calculated the correlation of miR-637 and DAPK3 expression in lung cancer (GSE19804) and found that the miR-637 expression level was significantly correlated with DAPK3 ($r=0.56$ and $p<0.001$), indicating that miR-637 expression may depend on the host gene DAPK3.

miR-637 is abnormally expressed in human cancers
As shown in Table 1, miR-637 expression was decreased in 18 cancers. Among them, the expression level of miR-637 in various cancer tissues was significantly lower than that in adjacent tissues, including glioblastoma and low-grade gliomas (GBM/LGG) [8–11], papillary thyroid carcinoma (PTC) [12, 13], non-small cell lung cancer (NSCLC) [14], gastric cancer (GC) [15–17], hepatocellular carcinoma (HCC) [18–21], CRC [22], pancreatic ductal adenocarcinoma (PDAC) [23], human cholangiocarcinoma (CHOL) [24], oral squamous cell carcinoma (OSCC) [25], prostate cancer (PCA) [26], ovarian cancer (OC) [27, 28], triple-negative breast cancer (TNBC) [29], cervical cancer (CCA) [30], osteosarcoma (SaOS) [31, 32], multiple myeloma (MM) [33], chronic myeloid leukemia (CML) [34]. In addition, the expression level of miR-637 was lower in the cell lines of various cancer cells than the corresponding normal cell lines, including PTC [12, 13], GC [17], HCC [18, 21], OSCC [35], PDAC [23], CHOL [36], TNBC [37], breast cancer (BRCA) [38], SaOS [31], etc. In the serum of CHOL patients, the expression level of miR-637 was lower than that of healthy people [39]. Notably, in the cancer tissues of clear cell renal cell carcinoma (ccRCC) patients, the expression level of miR-637 was higher compared with the adjacent tissues [40]. This may be due to the decreased expression of circHIPK3 in ccRCC tumors, which restores the expression of miR-637 [40].

Inhibitory effect of transcription factor ZEB2 on miR-637 expression
ZEB2, an EMT-related transcription factor, is closely associated with poor prognosis and malignant phenotype of tumors [41]. In GBM/LGG, ZEB2 can directly bind to two ZEB2 binding sites (CACCT) in the promoter region of miR-637, thereby inhibiting miR-637 and promoting the malignant phenotype of glioma [42].

The effect of miR-637 on cell behaviors
Repression of protein-coding genes by miRNAs can also modulate various cancer cell behaviors [43]. As shown in Fig. 1 and Table 2, miR-637 can target and inhibit multiple genes, thereby regulating cell growth, cell cycle, cell proliferation, EMT, cancer cell invasion, and metastasis. There are 21 downstream target genes of miR-637, including 3 genes related to cell growth (AKT1, leukemia inhibitory factor (LIF), and NUPR1), etc. In the serum of CHOL patients, the expression level of miR-637 was lower than that of healthy people [39]. Notably, in the cancer tissues of clear cell renal cell carcinoma (ccRCC) patients, the expression level of miR-637 was higher compared with the adjacent tissues [40]. This may be due to the decreased expression of circHIPK3 in ccRCC tumors, which restores the expression of miR-637 [40].

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Table 1  General downregulated expression of miR-637 in different cancers

| Systems       | Diseases          | Expression | Level                                     | Normal Group                                                                                                      | Disease Group                                                                                       | Ref |
|---------------|-------------------|------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----|
| Nervous       | GBM/LGG           | downregulated | tissue                                    | normal brain tissues from 15 healthy people                                                                      | 27 snap-frozen glioma tissues from 27 glioma patients                                                   | [9] |
|               |                   | downregulated | tissue                                    | adjacent normal brain tissues from 40 gliomas patients                                                            | glioma tissues from 40 gliomas patients                                                                     | [8] |
|               | GBM               | downregulated | tissue                                    | 28 non-neoplastic brain tissue samples                                                                           | primary GBM surgical specimens from 161 GBM patients                                                      | [11] |
|               |                   | downregulated | tissue                                    | normal human astrocytes from healthy people                                                                     | GBM tissues from 71 GBM patients                                                                         | [10] |
| Endocrine     | PTC               | downregulated | cell                                      | Nthy-ori 3–1                                                                                                    | TPC-1, CGTH-W3, IHH-4, HTH83, and SW579                                                                  | [12, 13] |
|               |                   | downregulated | tissue                                    | adjacent normal tissues                                                                                        | PTC tissues from 54 PTC patients                                                                         | [12] |
|               |                   | downregulated | tissue                                    | homologous adjacent normal tissues                                                                               | paraffin-embedded tumor tissues from PTC patients                                                    | [13] |
| Respiratory   | NSCLC             | downregulated | tissue                                    | adjacent normal tissues                                                                                        | NSCLC tissues from 74 male and 49 female NSCLC patients                                                  | [14] |
| Digestive     | GC                | downregulated | tissue                                    | adjacent normal tissues                                                                                        | GC tissues from 30 GC patients                                                                          | [15] |
|               |                   | downregulated | tissue                                    | adjacent normal tissues                                                                                        | GC tissues from 30 male and 28 female                                                                    | [16] |
|               |                   | downregulated | cell                                      | GES-1                                                                                                           | BGC-823, CRL-5822, SGC-7901, and AGS                                                                    | [17] |
|               | HCC               | downregulated | tissue                                    | 10 of non-neoplastic and non-cirrhotic liver                                                                    | HCC tissue from 15 patients                                                                           | [19] |
|               |                   | downregulated | tissue                                    | normal liver tissues                                                                                             | HCC specimens from 52 patients                                                                        | [21] |
|               |                   | downregulated | cell                                      | MiHA                                                                                                            | HepG2, Hep3B, Bel7404, and Huh-7                                                                       | [22] |
|               |                   | downregulated | tissue                                    | adjacent normal tissue samples                                                                                   | HCC tissue samples from 63 patients                                                                     | [18] |
|               | CRC               | downregulated | tissue                                    | adjacent normal tissues                                                                                        | HCC tissues from 46 patients                                                                           | [20] |
|               | PDAC              | downregulated | tissue                                    | adjacent normal tissues                                                                                        | CRC tissues from 50 CRC patients                                                                        | [22] |
|               |                   | downregulated | cell                                      | HPDE                                                                                                            | PDAC tissues from 25 PDAC patients                                                                      | [23] |
| CHOL          |                   | downregulated | cell                                      | H69                                                                                                              | TFk-1, SNU-869, SSP-25, RBE, HuCCT1, and HuH28                                                         | [36] |
|               | OSCC              | downregulated | cell                                      | NOK                                                                                                              | OSCC-15, Tca8113, SCC-9, SCC-25, and HSC-2                                                            | [35] |
| Urinary       | PCa               | downregulated | tissue                                    | matched adjacent normal tissues                                                                                  | PCa tissues from 65 PCa patients                                                                        | [26] |
|               | ccRCC             | upregulated  | tissue                                    | matched adjacent normal renal tissues                                                                            | ccRCC tissues from 40 ccRCC patients                                                                    | [26] |
| Reproductive  | OC                | downregulated | tissue                                    | adjacent normal tissues                                                                                        | 10 OC tissue from OC patients                                                                         | [28] |
|               | TNBC              | downregulated | tissue                                    | para-carcinogenic tissues                                                                                        | TNBC tissues from 60 TNBC patients                                                                      | [29] |
|               |                   | downregulated | cell                                      | MCF-7                                                                                                            | MDA-MB-231                                                                                            | [37] |
|               | BRCA              | downregulated | cell                                      | MCF-10A                                                                                                          | MCF-7 and T-47D                                                                                        | [38] |
|               | CCA               | downregulated | tissue                                    | adjacent normal tissues                                                                                        | CCA tissues from 20 CCA patients                                                                        | [30] |
| Bone          | SaOS              | downregulated | tissue                                    | normal tissues from 10 SaOS patients                                                                             | SaOS tissues from 10 SaOS patients                                                                      | [31] |
|               |                   | downregulated | cell                                      | SW1353                                                                                                           | U2OS                                                                                                  | [32] |
|               | MM                | downregulated | tissue                                    | chondroma tissues                                                                                                | SaOS tissues from 12 SaOS patients                                                                      | [32] |
|               |                   | downregulated | tissue                                    | bone marrow specimens from 21 healthy donors                                                                   | bone marrow specimens from 36 MM patients                                                              | [33] |
|               | CML               | downregulated | plasma                                    | plasma from 42 patients respond to IM                                                                             | plasma from 66 patients non-respond to IM                                                              | [34] |

GBM glioblastoma multiforme, LGG low-grade glioma, PTC papillary thyroid carcinoma, NSCLC non-small cell lung cancer, GC gastric cancer, HCC hepatocellular carcinoma, CRC colorectal cancer, PDAC pancreatic ductal adenocarcinoma, CHOL human cholangiocarcinoma, OSCC oral squamous cell carcinoma, PCA prostate cancer, ccRCC clear cell renal cell carcinoma, OC ovarian cancer, TNBC triple-negative breast cancer, CCA cervical cancer, BRCA breast cancer, SaOS osteosarcoma, MM multiple myeloma, CML chronic myeloid leukemia, IM Imatinib
2 genes related to cell cycle (HEMGN and LIF), 15 genes related to cell proliferation, 11 genes related to apoptosis, 1 gene related to EMT (NUPR1), and 15 genes related to cancer cell invasion and metastasis.

The inhibitory effect of miR-637 on cancer cell growth
Oncogenic signaling pathways can enhance the metabolic level of cancer cells to meet the energy requirements for cancer cell growth [44]. miRNAs can affect the metabolism of cancer cells by inhibiting the AMPK signaling pathway [43]. For example, miR-3619-5p can inhibit fatty acid oxidation in cancer cells for energy [45]. miR-637 inhibits the growth of tumor cell lines and tumor growth in xenograft animal models by targeting HEMGN and LIF.

HEMGN encodes a hematopoietic-specific nuclear protein of unknown function. Overexpression of HEMGN in bone marrow cells promotes cellular expansion [47]. In PTC, miR-637 blocked the cell cycle progression of PTC cell lines (TPC-1 and SW579) by targeting HEMGN and inhibiting the PI3K/Akt signaling pathway. Among them, miR-637 has the most obvious blocking effect on the G1/S transition phase of the cell cycle [12].

LIF is the most pleiotropic member of the IL-6 cytokine family. LIF participates in various pathways such as JAK/STAT, MAPK, and PI3K, and plays various roles in different types of cells, including stimulating or inhibiting cell proliferation, differentiation, and survival [48]. In TNBC, miR-637 can block the cell cycle

The blocking effect of miR-637 on cancer cell cycle
Inactivation of tumor suppressor genes relaxes cell cycle arrest, which in turn leads to genomic instability and ultimately promotes cancer development [46]. miR-637 blocks cancer cell cycle progression by targeting HEMGN and LIF.

Fig. 1 The target genes of miR-637 and cell behaviors. miR-637 inhibits cell cycle, proliferation, growth, EMT progression, invasion, and migration, and induces apoptosis by targeting the 3’-UTR of protein-coding genes.
| Diseases       | Targets     | Effects in vitro | Cell lines          | Effects in vivo | Laboratory animals | Ref |
|---------------|-------------|------------------|---------------------|----------------|-------------------|-----|
| GBM/LGG       | AKT↑        | growth↓, invasion↓, and migration↓ | U251 and U87        | tumor growth↓  | nude mice          |     |
|               | HMGA1       | proliferation↓, invasion↓, and migration↓ | U251 and U87        | tumor growth↓  | nude mice          |     |
|               | CDX6        | proliferation↓ and invasion↓ | LN18                | —              | —                 |     |
| GBM           | WNT7A       | proliferation↓ | U251 and LN229      | tumor growth↓  | BALB/c mice (4 weeks) |     |
| PTC           | HEMGN       | cell cycle↓, proliferation↓, migration↓, and apoptosis↑ | TPC-1 and SW579     | tumor growth↓  | BALB/c mice (5 weeks) |     |
|               | AKT1        | proliferation↓, invasion↓, and migration↓ | TPC-1 and HTH83     | tumor growth↓  | female BALB/C nude mice (8–12 weeks) |     |
| TC            | KLK4        | migration↓ and apoptosis↑ | K1 and TPC-1        | tumor growth↓  | female BALB/C nude mice (5 weeks) |     |
| NSCLC         | —           | proliferation↓, invasion↓, and migration↓ | H1299 and HCC827    | —              | —                 |     |
| GC            | CALA        | apoptosis↑      | AGS                 | —              | —                 |     |
|               | APLN        | proliferation↓, invasion↓, and apoptosis↑ | SGC-7901           | —              | —                 |     |
|               | MMP19       | invasion↓ and migration↓ | BGC823 and MGCC803  | —              | —                 |     |
|               | AKT1        | invasion↓ and migration↓ | SGC-7901 and AGS   | —              | —                 |     |
| HCC           | LIF         | growth↓ and apoptosis↑ | HepG2 and Bel7404   | tumor growth↓  | female BALB/C nude mice (4–6 weeks) |     |
|               | USP21       | proliferation↓ and invasion↓ | HepG2 and Hep38     | —              | —                 |     |
|               | AKT1        | proliferation↓ and invasion↓ | Huh-7 and Sk-Hep-1  | —              | —                 |     |
|               | AKT1        | proliferation↓ and invasion↓, migration↓ | Huh7 and MHCC-97H  | —              | —                 |     |
| CRC           | NUPR1       | invasion↓ and migration↓ | HCT116 and HT29     | —              | —                 |     |
|               | WNT1        | invasion↓, migration↓, and apoptosis↑ | HCT116 and SW480    | —              | —                 |     |
| PDAC          | AKT1        | growth↓ and apoptosis↑ | Capan-2 and BaPC-3  | —              | —                 |     |
| CHOL          | L196E       | proliferation↓, invasion↓, migration↓, and apoptosis↑ | HuCCT1 and RBE     | tumor growth↓, metastasis↓ | nude mice |     |
| OSCC          | NUPR1       | proliferation↓ | QBC939              | —              | —                 |     |
|               | NUPR1       | growth↓, invasion↓, EMT↓, and apoptosis↑ | SCC-9 and H5C-2     | —              | —                 |     |
| ccRCC         | —           | invasion↑ and migration↑ | CaKi1 and ACHN      | —              | —                 |     |
| OC            | KLK4        | proliferation↓, invasion↓, and migration↓ | OVCAR-3 and H8910  | —              | —                 |     |
|               | PLXNB2      | proliferation↓, invasion↓, migration↓, and apoptosis↑ | SKOV3 and CAOV3     | tumor growth↓  | BALB/c nude mice (4–6 weeks) |     |
| TNBC          | LIF         | cell cycle↓, apoptosis↓, and autophagy↑ | MDA-MB-231          | tumor growth↓, metastasis↓ | female nude mice |     |
|               | AKT1        | proliferation↓ and migration↓ | BT-549 and MDA-MD-231 | tumor growth↓, migration↓, metastasis↓ | female BALB/C nude mice (8 weeks) |     |
|               | AKT3        | —              | SiHa and C-41       | tumor growth↓  | female BALB/C nude mice (4 weeks) |     |
| SaOs          | STAT3       | invasion↓ and migration↓ | U2OS and SW1353     | —              | —                 |     |
|               | HDAC4       | proliferation↓, invasion↓, and migration↓ | HOS and U2OS       | —              | —                 |     |
| MM            | NUPR1       | proliferation↓, apoptosis↓, and autophagy↓ | U266 and RPMI8226   | —              | —                 |     |
| CML           | ABL1        | proliferation↓ and apoptosis↑ | K562                | —              | —                 |     |

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progression of TNBC cell line MDA-MB-231 by inhibiting LIF expression. Specifically, miR-637 has the most obvious blocking effect in the G1 phase of the cell cycle, and miR-637 can also inhibit tumor growth and metastasis in nude mice [29].

The effect of miR-637 on cancer cell proliferation

Cell proliferation is strictly regulated in the normal body. When the signaling pathway that inhibits proliferation is disturbed, it will lead to abnormal cell proliferation and cause cancer [49].

miR-637 inhibits cell proliferation of cancer cells by targeting 15 target genes (Fig. 1). These miR-637-targeted genes include HMGAI [42], CDK6 [50], and WNT7A [10] in glioma, HEMGN in PTC [12], APLN in GC [15], USP21 in HCC [51], LY6E [36] and CTSB [24] in CHOL, NUPR1 in OSCC [25] and MM [33], HDAC4 in SaOS [32], ABL1 in CML [34], KLK4 in OC [28], PLXNB2 in OC [27], AKT1 in TNBC [37], PTC [13], and HCC [18, 20], AKT3 in TNBC [37], and RING1 in CCA [30].

miR-637 can also suppress the proliferation of NSCLC tumor cells, it is worth noting that the target gene of miR-637 in NSCLC has not been reported [14]. miR-637 can hinder the growth of various tumors in xenograft animals by inhibiting various genes. These xenograft animals include xenografted BALB/c mouse models of PTC (HEMGN [12], AKT1 [13]), TNBC (AKT1 [37]), OC (PLXNB2 [27]), thyroid gland carcinoma (TC) (KLK4 [52]), and xenografted nude mouse models of GBM (HMGAI [42]) and CHOL (LY6E [36]).

Promoting effect of miR-637 on cancer cell apoptosis

Apoptosis is programmed cell death that does not cause an inflammatory response and is an important form of cell death [53]. Apoptosis maintains the balance between cell death and cell survival, and aberrant apoptosis escape is an important feature of cancer cells [54].

miR-637 promotes cancer cell apoptosis by targeting 11 protein-coding genes (Fig. 1). miR-637 can promote the apoptosis of various cancer cells by inhibiting multiple genes. These apoptosis-related genes inhibited by miR-637 include HEMGN in PTC [12], KLK4 in TC [52], CALA [55] and APLN [15] in GC, LIF in HCC [21] and TNBC [29], WNT1 in CRC [56], AKT1 in PDAC [23], LY6E in CHOL [36], NUPR1 in OSCC [35] and MM [33], PLXNB2 in OC [27], and ABL1 in CML [34].

Inhibitory effect of miR-637 on epithelial-mesenchymal transition (EMT)

The process of differentiation of epithelial cells into mesenchymal cells is called EMT [57]. EMT is the first step in the invasion-metastatic cascade, in which epithelial cells lose adhesion and polarity and acquire a strong migratory capacity similar to mesenchyme [58]. miRNA can affect the EMT process and are closely related to tumorigenesis, metastasis, and treatment resistance [59]. By targeting NUPR1 and inhibiting the conversion of E-cadherin to N-cadherin, miR-637 inhibited EMT progression in OSCC cell lines (Tca8113 and SCC-9) and OSCC xenograft BALB/c nude mouse model [35].

Attenuating effect of miR-637 on cancer cell invasion and metastasis

Invasion of tumor cells into surrounding tissues and metastasis in blood vessels are important initial steps of tumor metastasis and are the main cause of high mortality in cancer [60]. miR-637 inhibits the invasion and metastasis of various cancer cells by targeting 15 target genes (Fig. 1). These genes include HMGAI in glioma [42], AKT1 in glioma [9], PTC [13], GC [17], and HCC [18, 20], HEMGN in PTC [12], APLN [15] and MMP19 [16] in GC, WNT1 in CRC [56], NUPR1 in CRC [22] and OSCC [35], LY6E [36] and CTSB [24] in CHOL, KLK4 [28] and PLXNB2 [27] in OC, and HDAC4 [32] and STAT3 [31] in SaOS.

Furthermore, miR-637 inhibited cancer cell invasion in glioma [50] and HCC [51] by targeting CDK6 and USP21, respectively. miR-637 also inhibited cancer cell metastasis of TC by targeting KLK4 [52]. In NSCLC, miR-637 inhibited cancer cell invasion and metastasis [14]. miR-637 can inhibit tumor metastasis in the CHOL xenograft nude mouse by targeting LY6E [36]. Notably, downregulation of circHIPK3 in ccRCC alleviated its repressive effect on the expression level of miR-637, thereby attenuating invasion and metastasis in Caki1 and ACHN cell lines [40].

miR-637 is involved in various cancer-related signaling pathways

As shown in Fig. 2, miR-637 can regulate four signaling pathways, thereby inhibiting the occurrence and development of cancer. The signaling pathways associated with miR-637 in cancer include the Wnt/β-catenin signaling pathway [26], the Wnt/β-catenin signaling pathway [56], the ERK signaling pathway [61], and the PI3K/AKT signaling pathway [12].

The Jak/STAT3 signaling pathway

In the tumor microenvironment, the Jak/STAT3 signaling pathway drives tumor cell proliferation, survival, invasion, and metastasis, and suppresses anti-tumor-related immune responses [62]. IncAMPC can bind to histone H1.2 and promote the transcription of LIFR [26], LIF activates Jak upon its binding to the LIFR receptor on the extracellular plasma membrane, thereby promoting
the phosphorylation and dimerization of STAT3 into the nucleus, activating the signaling pathway [26]. Meanwhile, in CRC, low expression of miR-637 leads to activation of the Jak/STAT3 signaling pathway through the lncAMPC/miR-637/LIF axis, thereby promoting inflammation and cancer cell migration and invasion [6, 26].

**The Wnt/β-catenin signaling pathway**

The WNT/β-catenin signaling pathway regulates embryonic development, cell proliferation, and differentiation [63]. Wnt1 and Wnt7, encoded by miR-637 targets WNT1 and WNT7A, can coil Frizzled (FZDs) family receptors and recruit Dvl1 to activate the Wnt/β-catenin pathway [63]. In cancer, low levels of miR-637 lead to up-regulation of Wnt1 in CRC [56] and Wnt7 in GBM [10] and activate the Wnt/β-catenin pathway, thereby promoting cancer cell invasion, metastasis, metabolism, and inflammation [64].

**The ERK signaling pathway**

The ERK pathway is associated with cell proliferation, differentiation, migration, senescence, and apoptosis [65].
The polypeptide growth factor EGF activates the membrane tyrosine kinase HER2 by binding to the receptor EGFR on the plasma membrane, prompting MEK phosphorylation and Erk1/2 diphosphorylation, thereby activating the ERK signaling pathway [61]. In HER2-positive BRCA, miR-637 can down-regulate HER2, inhibit MEK phosphorylation and Erk signaling pathway, and ultimately promote cell apoptosis and inhibit proliferation and differentiation [61].

The PI3K/AKT signaling pathway
Aberrant activation of the PI3K/AKT pathway in cancer leads to cellular competitive growth advantage, metastatic capacity, angiogenesis, and therapeutic drug resistance [66]. HEMGN can recruit and activate AKT on the plasma membrane by promoting the phosphorylation of PI3K and the generation of PIP3, resulting in the activation of the PI3K/AKT signaling pathway [12]. NUPR1 can inhibit PTEN, a negative regulator of AKT, and phosphorylate PI3P [67], which in turn promotes AKT phosphorylation and activates the PI3K/AKT signaling pathway [68]. Low expression of miR-637 leads to up-regulation of the expression levels of HEMGN in PTC [12], NUPR1 in OSCC [35], and AKT1 in glioma [9, 69] and PDAC [23], thereby activating the PI3K/AKT signaling pathway and inhibiting the reproduction and growth of cancer cells.

The miR-637-related ceRNAs
CircRNAs and lncRNAs act as ceRNAs of miR-637 on its target mRNAs and play important roles in various biological processes of cancer. The circPSMA1/miR-637/AKT1 axis in TNBC enhances the proliferation and migration ability of TNBC cell lines and promotes tumor metastasis in BALB/c mice [37]. The circERBB2/miR-637/MMP19 axis in GC enhances the invasive and migratory abilities of GC cell lines [16]. In OC, the circ_0051240/miR-637/KLK4 [28] and the circ_0013958/miR-637/PLXNB2 axis [27], promote the malignant phenotype of OC cell lines. The circ_0039053/miR-637/USP21 axis in HCC promotes the proliferation and migration ability of HCC cell lines [51]. In PTC, the circPSD3/miR-637/HEMGN axis promotes the proliferation, migration, and cell cycle progression of PTC cell lines, and inhibits apoptosis [12]; in addition, the circHIPK3/miR-637/AKT1 axis in GC [17], the circHIPK3/miR-637/NUPR1 axis in OSCC [35], and the circHIPK3/miR-637/STAT3 axis in SaOS [31] are associated with cancer progression. In CRC, the IncFAL1/miR-637/NUPR1 axis promotes the invasion and migration of CRC cell lines [22, 78]. In HCC, the NIFK-AS1/miR-637/AKT1 axis enhanced the proliferation, invasion, and migration of HCC cell lines [18]. In OSCC, the LINC01234/miR-637/NUPR1 axis promotes the proliferation of OSCC cell lines [25]. In CaCa, the C5orf66-AS1/miR-637/RING1 axis enhances the proliferative capacity of CaCa cell lines and tumor growth in nude mice [30]. In TC, the HOTTIP/miR-637/AKT1 axis [13] and the PANDAR/miR-637/KLK4 axis [52], promote the malignant phenotype of TC cell lines. In glioma, the LINC00473/miR-637/CDK6 axis promotes the proliferation and invasion of glioma cell lines [50]. The IncAMPc/miR-637/LIF axis in Pca [26], HOTTIP/miR-637/LASPI axis in CHOL [39], LOC646616/miR-637 axis in essential hypertension [79], exert oncogenic effects in cancer. Notably, only in ccRCC, circHIPK3 expression was decreased, leading to up-regulation of miR-637 levels, which promoted the invasion and migration of Caki1 and ACHN cell lines [40].

Prognostic value of miR-637
The dysregulated expression of miR-637 is closely related to the clinicopathological features of cancer. As shown in Table 4, existing data confirmed that in GBM/LGG, NSCLC, HCC, and ovarian cancer (OV), low expression of miR-637 was closely associated with poor patient prognosis, suggesting that miR-637 could be used as a biomarker for cancer prognosis. In GBM/LGG, low expression levels of miR-637 and high expression of AKT1 generally represent tumor progression and are associated with poorer overall
survival (OS) and higher clinical stage [9]. In GBM, low expression of miR-637 and high expression of its target CYBRD1 were associated with poorer OS [11]. In NSCLC, lower levels of miR-637 were associated with lower OS and later tumor node metastasis (TNM) stage [14]. In HCC and OV, low levels of miR-637 predict lower OS in patients [51, 80].

Besides, the ceRNA networks of miR-637 also have a high clinical value. In HCC, circ_0039053/miR-637/USP21 axis usually predicts a higher TNM stage, lymph node metastasis, and lower OS in patients [51]. NIFKAS1/miR-637/Akt1 axis generally indicates lower OS and disease-free survival (DFS) in HCC patients [18]. In CRC, circHIPK3/miR-637/STAT3 axis is associated with lower OS and DFS, larger tumor volume, higher probability of regional lymph node metastasis, distant metastases, and poor recovery [6]. In TNBC, circSEPT9/miR-637/LIF/STAT3 axis is

| ceRNA axes | Diseases | Binding site of ceRNA and miR-637 | Binding site of miR-637 and PCG | Ref |
|------------|----------|---------------------------------|-------------------------------|-----|
|            |          | (5'…‑3')                        | (3'‑…‑5')                     |     |
| circ_0001947/miR-637 | NSCLC | —                               | —                             | [75]|
| circ_0013958/miR-637/PLXNB2 | OC     | —                               | —                             | [27]|
| circ_0051240/miR-637 | HCC    | CCCCCAG                         | GGGGGUC                       |     |
| circ_0039053/miR-637 | CML    | GACCCC                          | UGGGGG                       |     |
| circ_0051886/miR-637/ABL1 | GBM/LGG | CCCGccuCCCCCAG                 | GGGGucuGGGGGUC               | [8] |
| circEPHB4/miR-637/SOX10 | OC      | —                               | —                             | [16]|
| circCERBB2/miR-637 | HCC    | GCAAA C CUG GGG gcUUU         | —                             | [6]  |
| circHipK3/miR-637/ABL1 | GBM/LGG | CCCGGccuCCCGC                 | GGGGGccuGGGGGUC              | [18]|
| circHIPK3/miR-637/STAT3 | CRC    | GACcccGcaAAA                   | UGGGGGccuGGGGGUC            | [6]  |
| circPSD3/miR-637 | PTC    | CCCCCAG                         | GGGGGUC                      |     |
| circPSMA1/miR-637 | TNBC   | AGGGGGGUC                       | —                             | [37]|
| circUBR4/miR-637 | AS     | CCCCCCAG                       | —                             | [77]|
| circUSP36/miR-637/WNT4 | CCo    | CCCCCAG                         | CCCCCCAG                      | [30]|
| C5orf66-AS1/miR-637/RING1 | HSCR   | GGCTgggtcgCCCGC                | CCCCCCAG                      | [78]|
| FAL1/miR-637/ACT1 | CHOL   | GAGCGGGGAGA                    | —                             | [39]|
| HOTTIP/miR-637/LASP1 | PTCL   | GuAaAuauuGCAGGAGAGGUC         | —                             | [13]|
| HOTTIP/miR-637 | PCa    | GtAtttAcAtCCCCCAG              | CggggTtTGGGGGTCA             | [26]|
| IncAMPC/miR-637 | GVM/LGG | AGACCGGGAGACCGCCCGCAG         | CCCCCCAG                      | [50]|
| LINCO0473/miR-637/CDK6 | OSCC    | CCCCCCAGAG                     | —                             | [25]|
| LINCO1234/miR-637/NUPRT1 | EH     | ACAAuCCAgcaCCCGCAG            | —                             | [79]|
| LOC646616/miR-637 | HCC    | CCCCAGA                         | GGGGGCU                      | [18]|
| NIFK-AS1/miR-637 | TC     | AAAACAG                         | —                             | [52]|
| PANDAR/miR-637/SLK4 | PCa    | GGGGGGUC                       | —                             | [51]|

PCG protein-coding gene, NSCLC non-small cell lung cancer, OC ovarian cancer, EH essential hypertension, HCC hepatocellular carcinoma, CML chronic myeloid leukemia, GBM glioblastoma multiforme, LGG low-grade glioma, GC gastric cancer, OSCC oral squamous cell carcinoma, PTC papillary thyroid carcinoma, TNBC triple-negative breast cancer, AS atherosclerosis, CCa cervical cancer, HSCR Hirschsprung’s disease, CHOL human cholangiocarcinoma, PCa prostate cancer, TC thyroid gland carcinoma

Table 3 The binding sites of ceRNAs on miR-637
associated with a higher TNM stage and lower OS in patients [29]. In PCa, IncAMPCLIF/ LIF/LIFR axis predicts a higher tumor metastasis rate and lower relapse-free survival (RFS) in patients [26].

miR-637 and drug resistance in cancer cells
As shown in Fig. 4, abnormally low expression of miR-637 was associated with the resistance of cancer cells to three anticancer drugs dFdC, cisplatin (DDP), and OXA.
dFdC is the most important low molecular weight cytidine analog since cytarabine (Ara-C) [81]. DDP is a neutral square planar coordination complex of platinum (II), which is widely used in the treatment of various cancers [82]. dFdC-DDP is currently the standard therapy for advanced biliary tract cancer, but the generation of drug resistance is still an important problem in clinical treatment [83, 84]. LASP1 is a multifunctional protein that plays an important role in cytoskeleton formation [85]. LASP1 inhibits the sensitivity of cancer cells to chemicals [86]. In CHOL, miR-637 significantly inhibited the expression level of LASP1, which in turn enhanced the sensitivity of QBC939 and CCLP-1 cells to dFdC and DDP [39]. The level of miR-637 was competitively inhibited by its molecular sponge lncHOTTIP, resulting in the resistance of cancer cells to dFdC and DDP [39].

OXA is a third-generation platinum-based anticancer drug, mainly used for the treatment of CRC [87]. miR-637 can inhibit the expression of STAT3, thereby inhibiting the activation of the STAT3 signaling pathway, resulting in a decrease in the level of downstream Bcl-2, an increase in the level of beclin1, and enhancement of autophagy. The level of miR-637 was competitively inhibited by its molecular sponge circHIPK3, resulting in the resistance of HT29 and HCT116 cells to OXA [6].

**Discussions**

Various ceRNAs are aberrantly expressed in cancer, and multiple studies have exploited the interrelationships among dysregulated lncRNAs, circRNAs, miRNAs, and mRNAs to construct cancer-associated ceRNA networks [88]. The study of the ceRNA network helps to predict pathological changes in cancer patients and provides new molecular markers for prognosis [89, 90].

miR-637 is a potential cancer biomarker with diagnostic and prognostic value. The expression level of miR-637 in cancer cells or tissues was generally lower than that in corresponding normal cells or tissues, and the expression level of miR-637 was only up-regulated in ccRCC. Low expression of miR-637 is closely associated with poor prognosis in GBM/LGG, NSCLC, HCC, and OV cancer patients. An increasing number of studies have shown that miR-637 exerts tumor suppressor effects through

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**Fig. 4** The roles of miR-637 in the development of drug resistance. The low expression of miR-637 leads to the resistance of cancer cells to chemotherapeutic drugs, including OXA, dFdC, and DDP, by affecting the levels of a series of downstream proteins.
multiple pathways in most cancers (except ccRCC). miR-637 can directly target the 3'-UTR of 21 target genes, participate in at least 5 signaling pathways (Jak/STAT3, Wnt/β-catenin, PI3K/AKT, and ERK), and regulate the complex ceRNA axis and related network. miR-637 blocks the cell cycle in most cancers (except ccRCC), inhibits cancer cell growth, proliferation, EMT, invasion, and metastasis, and inhibits tumorigenesis and progression. Meanwhile, miR-637 also played a regulatory role in the resistance of cancer cells to three anticancer drugs (dFdC, DDP, and OXA).

The host gene of miR-637, DAPK3, is a nuclear protein kinase involved in apoptosis [91]. However, there is still no research on the relationship between the expression and function of miR-637 and DAPK3 in cancer. An in-depth study of the relationship between miR-637 and DAPK3 may broaden the understanding of the molecular mechanism of DAPK3 in cancer.

miRNAs are generally believed to localize to the cytoplasm to regulate translation [36]. However, emerging research has found that miRNAs can also exert transcellular regulatory roles in the form of exosomes. For example, cancer-associated fibroblasts regulate cellular metabolism in prostate and pancreatic cancers through miRNA-containing exosomes [92]. In addition, the upstream ceRNAs of miR-637 (circPSMA1 and circ_0000284) were upregulated in exosomes, thereby affecting the malignant phenotype of cells [36, 37]. This may be how miR-637 affects Jak/STAT3 and WNT signaling, but more data are still needed to support this hypothesis.

At present, the relationship between miR-637 in CRC and CHOL and some anticancer drugs has been studied. There are still a lot of deficiencies in the research on the role of miR-637 and different drugs, such as the role of miR-637 in other cancer treatment processes, etc. In future studies, changes in the expression of miR-637 during chemotherapy treatment in other cancers will be monitored to explore the role of miR-637 in cancer patient prognosis. Further research with an expanded sample size should be conducted on different cancer patients and different drug regimens, to better understand the relationship between the abnormal expression of miR-637 in cancer and the effect of drug treatment.

Conclusions
This work provides a systematic overview of miR-637, points out the potential of miR-637 to become a hot spot in cancer research, and provides clues and directions for subsequent research on miR-637. In the future, it is necessary to further study the molecular mechanism of miR-637 and its impact on the efficacy of tumor therapeutic drugs, so as to lay a theoretical foundation for the clinical targeted therapy of miR-637 in tumors.
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