REVIEW

Functional mechanism and clinical implications of MicroRNA-423 in human cancers

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Abstract
MicroRNAs play a vital role in the regulatory mechanisms of tumorigenesis. Current research indicates that microRNA-423 (miR-423) is abnormally expressed in various human tumors and participates in multiple signaling pathways of cancer progression. In most studies, miR-423 was confirmed as oncomiR, while a few contradictory reports considered miR-423 as an anticancer miRNA. The paradoxical role in cancer may hinder the application of miR-423 as a diagnostic and therapeutic target. Simultaneously, the interaction mechanism between miR-423 and lncRNA also needs attention. In this review, we have summarized the dual role of aberrant miR-423 expression and its mechanisms in tumorigenesis, and the therapeutic potential of miR-423 in human tumors.

KEYWORDS
clinical implications, functional mechanism, MicroRNA-423, tumorigenesis
1 | BACKGROUND

Human cancer is a major public health concern worldwide. Researchers have accumulated a wealth of knowledge about a complex network of multifunctional regulatory factors that form the basis of cancer progression and the underlying mechanisms, such as sustained proliferation regulation, evading immune surveillance, oncogenes overexpression, inhibition of apoptosis, and the interaction with proteins that play a synergistic effect in carcinogenesis and metastasis.\(^{2,3}\)

Dysregulation of microRNAs (miRNAs) in human cancers has been significantly involved in various signaling pathways and the pathogenesis.\(^{4-6}\) These molecules are a type of small non-coding RNA, which regulate the expression of certain protein-coding genes.\(^{7,8}\) MiRNAs function as transcriptional regulators by forming RNA-induced silencing complexes or as competitive endogenous RNAs (ceRNA).\(^{9,10}\) That specific regulatory mechanisms of miRNAs may affect tumorigenesis and may be potential targets for gene therapy.\(^{11}\) MiRNAs usually act post-transcriptionally by base pairing with the 3'untranslated region of the mRNA to regulate protein synthesis.\(^{12}\) The binding sites of miRNA targeting mechanism miRNAs are enriched, which endows miRNA itself with strong and specific feedback regulation ability to miRNA targeting activity, that is, the fragment-specific feedback of miRNA pathway is automatically regulated, complementary with transcription factors to form a mixed feedback loop.\(^{13}\) Exosomes are membrane-derived vesicles (30–100 nm) secreted in body fluids, which can selectively transmit miRNA through intercellular communication. exosomal-derived miRNAs are transferred to receptor cells, and they regulate the expression of target genes,\(^{14}\) and they also can participate in the development of chemical resistance.\(^{15}\) There is much evidence that dysregulated expression of various miRNAs in cells can ultimately enhance chemoresistance by affecting cell survival, apoptosis, and autophagy, thereby pushing normal cells toward cancerous cells.\(^{16}\) In some cases, aberrant expression of miRNAs has been shown to be associated with tumor metastasis. These miRNAs regulate metastasis by regulating the formation of metastatic niches and by regulating their target genes for metabolic reprogramming.\(^{17}\) As regulators of the human genome,\(^{18}\) the vast majority of miRNAs are located in cancer-related genomic regions and participate in tumor progression in the form of tumor suppressor genes or proto-oncogenes.\(^{19}\) In addition, some miRNAs have been identified as clinical biomarkers of certain human cancers.\(^{20,21}\) Further elucidation of the associations between miRNAs and carcinogenesis as well as clarification of the underlying mechanisms may contribute to an in-depth understanding of the mechanisms of cancer development and highlight therapeutic targets for use in the clinic.\(^{22}\)

MicroRNA-423 (miR-423) is located at 17q11.2 of chromosome 17 (gene coding ID: 494335). Two mature sequences (namely miR-423-3p and miR-423-5p) of the miRNA-423 gene were identified by searching the miRBase sequences.\(^{23-25}\) Previous studies have confirmed the differential expression of miR-423 in various human tumors,\(^{26}\) and also indicated differences in the functional mechanisms in different tumor types.\(^{27,28}\) In this article, we briefly review the latest reports on the functional mechanisms of miR-423 in tumors and its involvement in signaling pathways. The potential value of single nucleotide polymorphisms (SNPs) in pre-miR-423 (rs6505162) as a diagnostic biomarker, and a therapeutic target, are also discussed.

2 | THE FUNCTIONAL MECHANISMS OF MiR-423 IN DIFFERENT CANCERS

MiRNA dysregulation is caused by genetic factors and epigenetic changes.\(^{29}\) MiRNAs are engaged in fundamental cellular processes that involve evolutionarily conserved cascade reactions.\(^{22}\) MiR-423 can function as an suppressor or oncogene in cancer via a large number of direct and indirect regulatory target genes (Table 1). Numerous studies have indicated that miR-423 has different expression patterns and distinct functions in cellular processes such as cell proliferation and cell cycle, cell autophagy and apoptosis, tumor metastasis, and chemoresistance. Therefore, miR-423 is implicated as a good target for further investigations aimed at designing novel therapeutic strategies to manage tumors.

2.1 | Mechanisms of miR-423 in tumor cell proliferation and the cell cycle

The ability to maintain unrestricted cell proliferation is a hallmark of human tumors.\(^{22,30}\) The uptake of exosomes rich in miR-423-5p by cancer cells leads to gastric cancer progression by directly targeting the suppressor of fused protein(SUFU).\(^{31,32}\) Deletion of Tgfα factor 1 (TFF1) protein promotes β-catenin activation and gastric tumorigenesis,\(^{33}\) while miR-423-5p expression targets negative regulation TFF1 expression and participated in proliferation and metastasis-related processes of gastric cancer cells.\(^{34}\) Furthermore, inhibition of miR-423-5p expression upregulates gene associated with GRIM-19 expression and decreases BCL-2 expression to inhibit prostate cancer cell proliferation and promote apoptosis.\(^{35}\) Pre-miR-423-12C treatment inhibited breast cancer (BC) cell proliferation to a greater extent than pre-miR-423-12A, resulting in the proliferative capacity in the pre-miR-423-12C BC group was worse than that in the pre-miR-423-12A group.\(^{36}\) Furthermore, the miR-423 chain promotes BC cell growth by enhancing the expression of mutant p53 and proliferating cell nuclear antigen (PCNA).\(^{36}\)
| Tumors type                          | miR-423 form | miR-423 expression alteration and functional effects | Function or validated targets               | Biological functions of                                                                 | References |
|-------------------------------------|--------------|------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------|------------|
| Gastric cancer (GC)                 | miR-423-5p   | Up, carcinogenic                                      | SUFU(−)                                   | Cell proliferation and metastasis(+)                                                  | 31         |
|                                     | miR-423-5p   | Up, carcinogenic                                      | TFF1(−)                                   | Cell proliferation and invasion(+)                                                  | 34         |
|                                     | miR-423-3p   | Up, carcinogenic                                      | Bim(−), Beclin-1(+) and Atg 7(−)          | Cell proliferation, migration and invasion(+), autophagy(−)                      | 52         |
|                                     | miR-423-5p   | Down, anti-cancer                                     | β-catenin Interference(+)                 | Cell proliferation(−), apoptosis(+), sensitivity to 5-fluorouracil(+)              | 50         |
| Hepatocellular carcinoma (HCC)      | miR-423      | Up, carcinogenic                                      | p21Cip1/Waf1(−)                           | Cell growth and regulates G1/S transition(+)                                         | 25         |
|                                     | miR-423-5    | Up, carcinogenic                                      | ATG7(+), pErk-1/2 and AKT(−)              | Cell proliferation(+), autophagy(−), chemoresistance(+), apoptosis(+)            | 44         |
|                                     | miR-423      | Up, carcinogenic                                      | BRMS1(−)                                  | Cell invasiveness(+)                                                               | 56         |
| Glioblastomas (GBM)                | miR-423      | Up, carcinogenic                                      | ING-4(−), p-AKT and p-ERKJ2/2(+)          | Cell proliferation, angiogenesis, invasion, chemoresistance(+)                      | 37         |
|                                    | miR-423-3p   | Up, carcinogenic                                      | PANX2(−)                                  | Cell proliferation and apoptosis(+)                                                | 46         |
|                                    | miR-423-5p   | Up, carcinogenic                                      | mitochondrial pathway(+), Bax/Bcl-2 and cytochrome c(+), Apaf-1 and caspase-3(+) | Cell apoptosis(−), cell growth(+), sensitivity to apigenin(+)                       | 47         |
|                                    | miR-423-5p   | Down, anti-cancer                                     | PLCB1(−), p-ERK(+)                        | Cell Proliferation and metastasis(−), apoptosis(+)                                | 48         |
| Laryngeal carcinoma (LYC)           | miR-423-3p   | Up, carcinogenic                                      | AdipoR2(−)                                | Cell proliferation, clonogenicity, migration and invasion(+)                      | 57         |
| Lung adenocarcinoma (LAD)           | miR-423-5p   | Up, carcinogenic                                      | MTSS1(−)                                  | Colony formation, cell motility, migration and invasion(+)                        | 60         |
| Lung cancer (LC)                    | miR-423-3p   | Up, carcinogenic                                      | TDP-43 regulates(+)                       | Cell proliferation, migration and invasion(+)                                      | 58,59      |
| Colorectal cancer (CRC)             | miR-423-5p   | Down, anti-cancer                                     | caspases 3, 8 and 9, p53 (+); caspase-dependent | Cell apoptosis(+), cancer growth(−)                                                 | 49         |
|                                    | miR-423-5p   | Down, anti-cancer                                     | LAMC1(+)                                  | Cell migration and invasion(−), genetic modifier                                    | 62,64      |
|                                    | miR-423-3p   | Up, carcinogenic                                      | p21Cip1/Waf1(−)                           | Cell cycle and cell proliferation(+)                                              | 43         |
| Breast cancer (BC)                  | miR-423      | Up, carcinogenic                                      | PCNA and mutant p53(+)                    | Cell proliferation(+)                                                              | 36         |
|                                    | miR-423      | Up, carcinogenic                                      | ZFP36(−), Wnt /β-catenin(+)               | Chemoresistance(+), migration and proliferation(+), apoptosis(−)                   | 68         |
|                                    | miR-423      | Up, carcinogenic                                      | TNIP2(−), NF-κB signaling pathway(+)      | Invasiveness(+)                                                                     | 64         |
| Ovarian cancer (OC)                 | miR-423-5p   | Down, anti-cancer                                     | -                                        | Cell proliferation, colony formation and invasion(−)                              | 38         |
| Endometrial cancer (EC)             | miR-423      | Up, carcinogenic                                      | caspase 3/7 and Bcl-2(−), PTEN(−) and p-AKT(+) | Cell proliferation, migration and invasion(+), EMT(+), chemoresistance(−), apoptosis(−) | 45,55      |
| Prostate cancer (PC)                | miR-423-5p   | Up, carcinogenic                                      | GRIM-19(−), BCL-2(+)                     | Proliferation(+), apoptosis(−)                                                     | 35         |

(Continues)
TABLE 1 (Continued)

| Tumors type       | miR-423 form | miR-423 expression alteration and functional effects | Function or validated targets | Biological functions of | References |
|-------------------|--------------|-----------------------------------------------------|-------------------------------|-------------------------|------------|
| Osteosarcoma      | miR-423-5p   | Down, anti-cancer                                    | STMN1(−)                      | Cell proliferation, colony formation and invasion(+) | 40         |
| Cervical cancer (CC) | miR-423-3p   | Down, anti-cancer                                    | Endogenous E6/E7-regulated(+)  | Cell proliferation(+), senescence and apoptosis(−)   | 39         |

Abbreviations: (−), suppression and reduction; (+), promotion and activation; AdipoR2, adiponectin receptor 2; Atg7, autophagy-related gene 7; Bim, Bcl-2-interacting mediator; BRMS1, breast cancer metastasis suppressor 1; EMT, epithelial-mesenchymal transition; FOSL2, FOS like 2, AP-1 transcription factor subunit; ING4, inhibitor of growth 4; LAMC1, laminin γ1; MTSS1, metastasis suppressor 1; p53, tumor protein 53; PANX2, pannexin 2; PCNA, proliferating cell nuclear antigen; PLCB1, phospholipase C beta 1; PTEN, phosphatase and tensin homolog; SUFU, suppressor of fused homolog; TDP-43, TAR DNA binding protein 43; TFF1, trefoil factor 1.

Overexpression of miR-423-5p induces upregulation of p-ERK1/2 and p-AKT and enhances glioma cell proliferation, as well as angiogenesis and metastasis by targeting inhibitor of growth 4 (ING-4).37 MiR-423 has also been found to possess a tumor suppressor gene in a few studies, which can inhibit cell proliferation of tumors. Ectopic expression of miR-423-5p, as an anticancer miRNA, inhibits ovarian cancer cell proliferation and colony formation.38 Downregulation of miR-423-3p in exosomes secreted by HeLa cervical cancer cells results in E6/E7-dependent cell proliferation in HPV-positive cancer cells.39 MiR-423-5p mediated cell colony formation and proliferation in osteosarcoma by inhibiting stathmin1 (STMN1) expression.40 Thus, miR-423 is implicated as a therapeutic target to inhibit the proliferation of tumor cells and prevent tumor progression (Figure 1).

The normal cell division process involves a series of highly regulated cell cycle steps.30 Blockade of this process at certain stages can cause cancer.22 Bioinformatics analysis has pointed out that miR-423-5p mainly acted as oncomiR in tumors and involved in the cancer cell cycle.41 MiR-423-3p can also affect cell cycle progression by regulating ATP/energy metabolism.42 MiR-423-3p promotes the G1 phase to S phase cell cycle transition and inhibits the colorectal cancer cells proliferation by inhibiting p21Cip1/Waf1.43 MiR-423-3p has similar functional effects in hepatocellular carcinoma (HCC), whereas miR-423-5p does not.25 Interestingly, after miR-423-5p was up-regulated in HCC cells, it was found that the percentage of HCC cells in the S phase showed an increase.44 The ability of miR-423 to regulate the cell cycle in tumors remains to be clarified (Figure 1).

2.2 | Mechanisms of miR-423 in apoptosis and autophagy

Inhibition of apoptosis can promote tumor progression. Conversely, apoptosis induction can inhibit tumor progression.22 A study showed that miR-423 inhibits cisplatin-induced apoptosis by modulating the expression levels of caspase 3/7 and Bcl-2 in endometrial cancer cells.45 Pannexin 2 (PANX2), which is considered to be a target gene of miR-423-3p, is up-regulated in glioma cells when miR-423-3p is inhibited, leading to a reduction in glioma cell proliferation and the induction of apoptosis.46 Similarly, miR-423-5p targets inhibition of ING-4 to inhibit apoptosis of glioblastoma cells.47 Apigenin is a plant-derived flavonoid that participates in numerous signaling cascades in tumors.3 When combined with the inhibitory effect of miR-423-5p, apigenin-induced glioma stem cell apoptosis was significantly elevated.3,47 In-depth studies have shown that miR-423-5p enhances the induction of apoptosis by apigenin via the mitochondrial pathway and changes the expression of Bax/Bcl-2 and cytochrome c/Apaf-1/caspase-3.37 Inhibition of apoptosis by miR-423 in the above studies promoted tumor progression. On the contrary, miR-423 can also be used as anti-cancer miRNA to induce cancer cell apoptosis. For example, MiR-423-5p inhibits glioma metastasis by target phospholipase C beta 1 (PLCB1) via the ERK-dependent pathway, and also promotes apoptosis in glioma cells.48 Increased miR-423-5p expression induces the expression of caspase 3, 8, 9, and p53 in colon cancer cells, thereby inhibiting cell proliferation and promoting cell apoptosis.49 Similarly, Knockdown expression of β-catenin can downregulate miR-423-5p expression, thereby promoting gastric cancer apoptosis.50 Thus, these reports provide evidence that miR-423 influences the process of apoptosis in tumor cells (Figure 2).

Interventions to both stimulate and inhibit autophagy have been proposed as cancer therapies.51 So far, there have been few reports on miR-423 and autophagy in cancer. Treatment of liver cancer cells with sorafenib showed that miR-423-5p is a promoter of autophagy in HCC cells.44 MiR-423-3p activates carcinogenesis of gastric cancer cells and affects Beclin-1-dependent autophagy by downregulating Bim and Atg 7 expression.52 It can be speculated that more than one autophagy pathway is influenced by miR-423 in different tumors and therefore, further research is needed to elucidate the mechanism of miR-423 and cell autophagy in specific tumors (Figure 2).
**Figure 1** Schematic view of different roles of miR-423 in cancer cell proliferation and experiments have confirmed that miR-423 is involved in the regulation of cellular targets and pathways in tumor cell proliferation and cell cycle. Black font indicates that miR-423 acts as a carcinogenic miRNA effect in tumors; purple font indicates that miR-423 acts as a tumor suppressor miRNA effect in tumors. (Tumor name abbreviation: BC, breast cancer; CC, cervical cancer; CRC, colorectal cancer; EC, endometrial cancer; GBM, glioblastoma; GC, gastric cancer; HCC, hepatocellular carcinoma; LAD, lung adenocarcinoma; LC, lung cancer; LYC, laryngeal carcinoma; NPC, nasopharyngeal carcinoma; OC, ovarian cancer; PC, prostate cancer; PTC, papillary thyroid carcinoma.)

**Figure 2** Schematic view of different cancer roles of miR-423 in cell apoptosis and autophagy, and experimentally confirmed cellular targets and pathways of miR-423 in the cell apoptosis and autophagy. Black font indicates that miR-423 acts as a carcinogenic miRNA effect in tumors; purple font indicates that miR-423 acts as a tumor suppressor miRNA effect in tumors. (Tumor name abbreviation: BC, breast cancer; CC, cervical cancer; CRC, colorectal cancer; GBM, glioblastoma; GC, gastric cancer; HCC, hepatocellular carcinoma; LAD, lung adenocarcinoma; PC, prostate cancer.)
2.3 | MiR-423 and metastasis

MiR-423 is a common marker of transcarcinal metastasis in metastatic samples. Epithelial-mesenchymal transition (EMT) facilitates the smooth colonization of cancer cells in other target organs. Overexpression of miR-423 in endometrial cancer cells alters EMT and modulates the expression levels of PTEN and p-AKT, ultimately promoting the metastasis of endometrial cancer cells. Similarly, the miR-423-3p-Bim axis promotes GC cell metastasis. MiR-423 also significantly inhibited BRMS1 protein expression and exacerbated the aggressiveness of HCC. In laryngeal cancer, miR-423-3p has been confirmed to affect tumor cell metastasis by regulating AdipoR2. Furthermore, TAR DNA binding protein (TDP-43) promotes lung cancer cell metastasis by upregulating the expression of oncogenic miR-423-3p. In addition to these functions, miR-423-5p also significantly promotes colony formation, cell migration, invasion and distant brain metastasis in lung adenocarcinoma by inhibiting metastasis suppressor 1 (MTSS1) expression. Similarly, high miR-423-3p expression is also associated with an increased risk of brain metastases from lung adenocarcinoma. In addition, overexpression of miR-423-5p downregulates ING-4 expression in glioma tissues to enhance angiogenesis and promote glioma cell invasion. With this just the opposite is, MiR-423 can also act as a tumor suppressor in colon cancer. The upregulated MiR-423-5p can specifically bind and downregulate the expression of LAMC1, thereby inhibiting the migration of colorectal cancer cells. For another example, miR-423-5p overexpression inhibits osteosarcoma cell metastasis by inhibiting STMNI expression. Similarly, miR-423-5p directly targets PLCB1 expression in glioma to inhibit tumor cell metastasis. The latest research shows that abnormally high expression of miR-423 enhances the aggressiveness of breast cancer cells. Mechanistically, the up-regulation of miR-423 targets the inhibition of TNIP2 expression resulting in the activation of the NF-κB signaling pathway and the increased expression of *snails and twists*. Thus, it is clear that abnormal expression of miR-423 can affect cancer cell metastasis of human tumors, miR-423 may be a promising prognostic and therapeutic marker for patients with metastatic cancer. (Figure 3).

2.4 | MiR-423 and chemotherapy response

Resistance to chemotherapeutic drugs impairs the ability to cure cancer patients after relapse. In malignant tumors, Wnt/β-catenin signaling pathway can regulate certain miRNAs to participate in malignant tumor progression. Decreasing β-catenin expression downregulates miR-423-5p expression and reduces the resistance of gastric cancer cells to 5-fluorouracil. miR-423-5p may act as a tumor suppressor in gastric cancer, and upregulating its expression can increase the sensitivity of gastric cancer cells to 5-fluorouracil. Whole blood samples stored at room temperature for 24 hours had no significant effect on the concentration of miR-423-5p, indicating that serum miR-423-5p can be used as a biomarker for therapeutic response. In sorafenib-treated HCC, the upregulated levels of secreted miR-423-5p correlated positively with the sorafenib response. Concurrently, miR-423-5p transfected HCC cells can promote the regulation of autophagy. Ectopic miR-423-5p highly expression in gliomas is a potential tumor promoter, targets ING-4 expression, enhances the formation of glioblastoma neurospheres and confers resistance to temozolomide in glioma cells. Furthermore, knockdown miR-423-5p increases the sensitivity to apigenin-induced apoptosis in glioma stem cells, the combination of apigenin and miR-423-5p knockdown has an additive effect of promoting apoptosis and inhibiting cell proliferation. MiR-423 high expression induces the sensitivity of endometrial cancer cells to cisplatin by causing loss of PTEN and activation of AKT. Therefore, miR-423 is implicated as a predictive biomarker of cisplatin chemotherapy response in endometrial cancer. MiR-423 has been proved to be an oncogene that promotes the malignant breast cancer (BC) cells proliferation and migration, can inhibit the expression of ZFP36 in BC cells, and activate Wnt/β-catenin signaling pathway, ultimately affecting the chemoresistance and apoptosis rate of BC cells. Similarly, the abnormal exosomal miR-423-5p expression affects the therapeutic effect of cisplatin in triple negative BC. Meanwhile, circulating miR-423-5p may also serve as a potential biomarker for chemotherapy-related cardiac dysfunction in BC patients. There are few reports on the relationship between miR-423 and chemotherapy response in tumors. Thus, the association of miR-423 with chemotherapy resistance in other tumors remains to be clarified (Figure 4).

3 | THE REGULATORY MECHANISM OF MiR-423 AND LncRNA IN HUMAN TUMOR

Long noncoding RNA (lncRNAs) is a new regulator of genomic stability and human diseases. lncRNAs plays an essential role in maintaining embryonic stem cells pluripotency, coordinating the regulation of immune cell activation and heterochromatin formation. Many factors have been found to affect the expression and secondary structure of lncRNAs. The different processing and localization of lncRNA are the factors that lead to the rapid evolution of lncRNA’s functions, which contribute to the nonconservative functions of stem cells. Unstable transcripts associated with lncRNAs and promoters...
or enhancers are preferentially localized to chromatin, some of which regulate chromatin structure, transcription, and RNA processing. The data show that lncRNA potency can be closely related to lncRNA abundance. In the lncRNA targeted domain, Polycomb responsive complexes are recruited to CpG island through lncRNA independent mechanism, and then interact with lncRNA and its related proteins through three-dimensional space to make Polycomb responsive complexes diffuse and nucleate in lncRNA targeted domain. Many lncRNAs related to various types of cancer have been identified by genome-wide association studies of tumor samples. LncRNA expression mutations can promote tumor occurrence and metastasis. LncRNA also participates in the metabolic remodeling of tumor cells and promotes the rapid proliferation of cancer cells. Numerous studies have shown that lncRNAs can bind to miRNA sites as competitive endogenous RNAs.
| Tissue or cell type                     | LncRNA name (ceRNA yes or no) | LncRNA alteration and functional effects | LncRNA biological functions                                                                 | MiR-423 form and signal axis                        | miR-423 functional effects and expression alteration | References |
|----------------------------------------|-------------------------------|----------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------|-----------------------------------------------------|------------|
| Non-small cell lung cancer (NSCLC)     | MT1JP (ceRNA)                | Up, anti-cancer                        | Cell proliferation(−), cell migration and invasion(−), cell apoptosis(+)                  | miRNA-423-3p/Bim                                    | Carcinogenic, down                                   | 79         |
| Hepatocellular carcinoma (HCC)         | FENDRR (ceRNA)               | Down, anti-cancer                      | Cell proliferation and tumorigenicity(−), apoptosis(+/−), Treg-Mediated Immune Escape(−)   | miR-423-5p/GADD45B                                 | Carcinogenic, up                                     | 80         |
| Breast cancer (BC)                     | LINC00968 (ceRNA)            | Down, anti-cancer                      | Cell proliferation, migration and tube formation abilities, tumor growth(−)               | miR-423-5p/PROX1                                   | Carcinogenic, up                                     | 81         |
| Tongue squamous cell carcinoma (TSCC)  | CASC9 (ceRNA)                | Up, carcinogenic                       | Cell proliferation, migration and invasion(+)                                            | miR-423-5p/PROX1                                   | Anti-cancer, down                                    | 82         |
| Lung adenocarcinoma (LUAD)             | LOXL1-AS1 (ceRNA)            | Up, carcinogenic                       | Cell proliferation(+), cell migration and invasion(+), cell apoptosis(−)                  | miR-423-5p/MYBL2                                   | Anti-cancer, down                                    | 83         |
| Papillary thyroid carcinoma (PTC)      | NR2F1-AS1 (ceRNA)            | Up, carcinogenic                       | Cell proliferation(+), cell migration and invasion(+)                                    | miR-423-5p/PROX1                                   | Anti-cancer, down                                    | 84         |
| Ovarian cancer (OC)                    | LINC00319 (ceRNA)            | Up, carcinogenic                       | Cell proliferation(+), cell migration and invasion(+)                                    | miR-423-5p/NACC1 pathway                          | Anti-cancer, down                                    | 85         |
| Nasopharyngeal carcinoma (NPC)         | AFAP1-AS1 (ceRNA)            | Up, carcinogenic                       | Cell migration and invasion(+)                                                            | miR-423-5p, FOSL2/Rho/Rac signaling                | Anti-cancer, down                                    | 86         |
| Gastric cancer (GC)                    | LINC01606 (ceRNA)            | Up, carcinogenic                       | Cell migration and invasion(+)                                                            | miR-423-5p, Wnt3a/Wnt/beta-catenin signaling       | Anti-cancer, down                                    | 87         |
| Clear cell renal cell carcinoma (ccRCC)| LINC01426                    | Up, carcinogenic                       | Cell proliferation and migration(+)                                                       | IGF2BP1/CTBP1/HDAC2/miR-423-5p/FoxM1 axis          | Anti-cancer, down                                    | 88         |

Abbreviations: (−), suppression and reduction; (+), promotion and activation; Bim, BCL2-like 11; FOSL2, FOS like 2, AP-1 transcription factor subunit; FOXM1, forkhead box M1; GADD45B, growth arrest and DNA damage inducible beta; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; MYBL2, myb proto-oncogene like 2; NACC1, nucleus accumbens associated 1; PLCB1: phospholipase C beta 1; PROX1, prospero homeobox 1; SOX12, SRY (sex determining region Y) box 12; Wnt3a, Wnt family member 3A.
(ceRNAs), thereby regulating and affecting the expression of downstream target genes. These lncRNAs can play an important regulatory role in tumor pathogenesis through the lncRNA-microRNA-mRNA related ceRNA network.78

The regulatory role between miR-423 and LncRNA in tumors is mainly the ceRNAs mechanism, and we also give a brief overview of the related research progress (Table 2). In some studies, low expression of lncRNA in cancer tissues has been found to act as a tumor suppressor gene and inhibit tumor progression. LncRNA MT1JP inhibits the malignant phenotype of non-small cell lung cancer by regulating the miRNA-423-3p/Bim signaling axis.79 The lncRNA FENDRR inhibits miR-423-5p and upregulates GADD45B to reduce proliferation and tumorigenicity and promote apoptosis of hepatoma cells, thereby preventing Treg-mediated immune escape of liver cancer.80 LncRNA LIN00956 inhibits miR-423-5p expression in a concentration-dependent manner and mediates upregulation of prospero homeobox 1 (PROX1) to inhibit breast cancer progression, such as cell proliferation, migration, and tube-forming ability as well as tumor growth.81 miR-423 is highly expressed in the above studies and plays a role of carcinogenic (Figure 5).

With this just the opposite is, LncRNAs interacting with miR-423 are highly expressed in most tumor tissues and can promote tumor progression. LncRNA CASC9 is upregulated in tongue squamous cell carcinoma tissues and cells, suggesting that patients have poor prognosis and can influence the malignant process of tongue squamous cell carcinoma by regulating the miR-423-5p/SOX12 axis.82 The positive feedback loop of lncRNA LOXL1 antisense RNA 1(LOXL1-AS1)/miR-423-5p/MYBL2 in lung adenocarcinoma is carcinogenic, and The high expression of LOXL1-AS1 competitively inhibits miR-423-5p expression and targets MYBL2 to promote proliferation and migration, and inhibit apoptosis of lung adenocarcinoma cell.83 The highly expressed lncRNA NR2F1-AS1 regulates miR-423-5p/SRY-box 12 axis to promote papillary thyroid carcinoma cell proliferation and invasion.84 Upregulation of LINC00319 has carcinogenic effects and enhances the expression of nucleus accumbens associated 1 (NACC1) by inhibiting miR-423-5p, which then promotes ovarian cancer cells metastasis and proliferation.85 The lncRNA AFAP1-AS1 competitively inhibits miR-423-5p expression in nasopharyngeal carcinoma cells to regulate the Rho/Rac pathway, thereby mediating the expression of FOSL2 and ultimately, promoting the distant metastasis of nasopharyngeal carcinoma cells.86 The high expression of LINC01606 in gastric cancer (GC) liberates miR-423-5p bound to Wnt3a through a competitive endogenous RNA (ceRNA) mechanism, thereby upregulating Wnt3a expression and inhibiting the Wnt/β-catenin pathway to promote gastric cancer cell metastasis.87 LINC01426 is upregulated in the renal clear cell carcinoma (ccRCC) cell line, promoting the proliferation and migration of ccRCC cells.88 Mechanistically, LINC01426 upregulates FOXM1 expression by inhibiting miR-423-5p, while LINC01426 can recruit IGF2BP1 to increase CTBP1 expression. CTBP1 and HDAC2 can also inhibit miR-423-5p expression, while downregulated miR-423-5p can Targeted

FIGURE 5 Regulatory mechanism of miR-423 and LncRNA in human tumor. The regulatory roles of miR-423 and LncRNAs in tumors are mainly ceRNAs mechanism, which participate in cancer cell proliferation and growth, migration and invasion, apoptosis, immune escape and chemotherapeutic resistance by regulating multiple targets. Orange font indicates that lncRNA plays an Anti-cancer lncRNA effect in tumors and that miR-423 acts as an oncogenic miRNA; purple font indicates that lncRNA acts as a carcinogenic lncRNA effect in tumors and that miR-423 acts as a tumor suppressor miRNA. (Tumor name abbreviation: BC, breast cancer; ccRCC, clear cell renal cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; LAD, lung adenocarcinoma; LC, lung cancer; LUAD, Lung adenocarcinoma; NPC, nasopharyngeal carcinoma; NSCLC, Non-small cell lung cancer; OC, ovarian cancer; PTC, papillary thyroid carcinoma; TSCC, Tongue squamous cell carcinoma.)
upregulation of FOXM1 expression to promote the progress of ccRCC.\textsuperscript{88} In the above studies, it was found that the expression of miR-423 was often inhibited and played an anti-tumor role (Figure 5).

In summary, compared with miR-423-3p, the functions and molecular mechanisms of miR-423-5p in human tumors have been more extensively investigated and may be more important, although this speculation remains to be confirmed in studies. MiR-423 interacts with other biomolecules and participates in the tumor progression. Thus, miR-423 is implicated as a biological target for tumor therapy.

4 | PROGRESS IN SINGLE NUCLEOTIDE POLYMORPHISM (SNP) RESEARCH ON MiR-423 (rs6505162)

Due to the inherent cancer-specific heterogeneity, SNPs play a crucial role in the development of human tumors.\textsuperscript{89,90} A meta-analysis of miR-423 polymorphisms and cancer prognosis suggests that rs6505162 is a prognostic marker of all common human cancers.\textsuperscript{91} According to another meta-analysis, rs6505162 may participate in the prevention of cancers such as lung cancer and colorectal cancer, but does not reduce the risk of breast cancer, esophageal cancer and gastric cancer.\textsuperscript{92} These polymorphisms have the potential to lead to metabolic abnormalities and changes in cancer susceptibility (Table 3). The rs6505162 C>A polymorphism, mapping to chromosome 17 at 17q11.2, is situated in the pre-miRNA region of miR-423.\textsuperscript{27,93-96} The pre-miR-423 SNP can prevent endogenous processing of two mature forms of miRNA (miR-423-5p and miR-423-3p).\textsuperscript{36} It is widely believed that miRNA-SNPs exert biological functions through two main mechanisms: (a) by changing the specific sequence of the miRNA core region and altering the binding affinity between the miRNA and the mRNA; and (b) by affecting the mature modification process of miRNA and altering its expression.\textsuperscript{22}

Growing evidence supports the association between rs6505162 and the cancer risk of several cancers, as well as the susceptibility of individuals to cancer, although the results are contradictory.\textsuperscript{97-104} Pre-miR-423 SNP has been reported to affect mature miR-423 expression in cell lines derived from endometrial carcinoma\textsuperscript{105} and breast cancer\textsuperscript{36} tissues, and plays an oncogenic role in tumorigenesis.\textsuperscript{36} The rs6505162 SNP has been reported to affect the risk of esophageal cancer.\textsuperscript{106} Many reports have also linked rs6505162 to environmental exposure to cancer. A recent study conducted in South Africa indicated that rs6505162 is associated with environmental exposure to smoke and can increase the risk of esophageal squamous cell carcinoma.\textsuperscript{107} In addition to environmental factors, genetic factors (such as rs6505162) are also play carcinogenic roles in esophageal squamous cell carcinoma.\textsuperscript{108,109} Nevertheless, a recent study demonstrated that there is no correlation between any genetic model of miR-423 (including rs6505162) and susceptibility to esophageal squamous cell carcinoma.\textsuperscript{110} Similarly, there is no biological association between rs6505162 and passive smoking exposure in Chinese women with lung cancer.\textsuperscript{111} The rs6505162 SNP is associated with genetic susceptibility to lung cancer and lung adenocarcinoma.\textsuperscript{102} The rs6505162 SNP also has implications for the prognosis of patients with completely resected non-small cell lung cancer.\textsuperscript{112} Two recent meta-analyses, indicated that rs6505162 significantly decreased the risk of lung cancer, suggesting that this miR-423 polymorphism is an effective protective factor against lung cancer.\textsuperscript{104,113} Analysis using association methods revealed that the CC genotype of rs6505162 reduced the risk of breast cancer development.\textsuperscript{100} There are ethnic differences in susceptibility to breast cancer. An in silico analysis showed that the AC genotype is mainly associated with Europeans (57%), while Africans and Asians were mainly AA (about 60%) and CC (about 60%), respectively.\textsuperscript{114} The rs6505162 SNP was found to affect the risk of familial breast cancer in a study conducted in South America.\textsuperscript{99} Rah et al reported that breast cancer-related microRNA polymorphisms, including rs6505162, are connected with increased primary ovarian insufficiency risk via interactions with miR-423 A variants.\textsuperscript{115} Interestingly, a case-control study (7170 breast cancer and 8783 controls) showed no correlation between the various genetic models of miR-423 and the risk of breast cancer.\textsuperscript{116} Dozens of colorectal cancer susceptibility bases have been identified by genome-wide association analysis (GWAS), and rs6505162 has been shown to affect the prognosis of colorectal cancer patients following chemotherapy.\textsuperscript{53,117} Similarly, rs6505162 has been identified as a biomarker of colorectal cancer metastasis.\textsuperscript{118} Another study indicated that rs6505162 has a negative impact on susceptibility to Wilms tumor, especially in Chinese children.\textsuperscript{28} However, no significant associations were found in some cancers, such as bladder cancer.\textsuperscript{103} HCC,\textsuperscript{119} and gastric cancer/advanced gastric cancer.\textsuperscript{120,121} The miR-423 rs6505162 polymorphism is considered to be a tumor-related susceptibility gene. Functional characterization of the rs6505162 polymorphism as potentially harmful risk alleles helps clarify its function in complex diseases.

5 | CLINICAL IMPLICATIONS OF MiR-423 IN CANCER

MiRNA plays an irreplaceable regulatory role in the occurrence and development of tumors.\textsuperscript{122} Specific serum miRNA expression profiles can be used for early diagnosis of cancer as well as monitoring treatment efficacy.\textsuperscript{123}
| Cancer type | Year   | Country     | Sample size | Potential significance and sensitivity/specificity                                                                 | References |
|-------------|--------|-------------|-------------|---------------------------------------------------------------------------------------------------------------------|------------|
| Oesophageal squamous cell carcinoma (OSCC) | 2013   | South Africa | 368 cases and 583 controls | In Blacks, under dominant, additive and recessive models with odds ratios (ORs) 1.353, 1.404, and 2.858, respectively. (OR(GE) = 7.855, P(GE) = 9.17*10(−10) in the Black group). | 107        |
|             | 2017   | Iran        | 200 cases and 300 controls | Codominant (AA vs. CC, OR [95% confidence interval, CI]: 0.32 [0.15–0.69], p-value: 0.0076); recessive (AA vs. CC+CA, OR [95% CI]: 0.35 [0.16–0.73], p-value: 0.0027); log-additive models (OR [95% CI]: 0.69 [0.52–0.91], p-value: 0.0084). | 109        |
| Esophageal cancer (EC) | 2008   | USA         | 346 Case and 346 Control | Per-allele OR of 0.64 [95% confidence interval: 0.51–0.80; p < 0.0001]. | 106        |
| Esophageal squamous cell carcinoma (ESCC) | 2013   | China       | 629 cases and 686 controls | AA vs. CC/CA: adjusted OR = 4.94, 95% CI = 1.42–17.21, p = 0.012. | 108        |
|             | 2019   | Mixed       | 22 studies from 13 articles | No significant associations between the rs6505162 and the susceptibility of ESCC in any genetic model. | 110        |
| Breast cancer (BC) | 2012   | Australia   | 179 cases and 174 controls | The CC genotype reduced risk of breast cancer (OR = 0.50, 95% CI = 0.27–0.92, p = 0.03). | 100        |
|             | 2018   | United Kingdom | European 97, Asian 90, African 90. | 57% Europeans associated with AC genotype, while approx. 60% Asians display mostly associated with CC genotype, and approx. 60% Africans mainly associated with AA genotype. | 114        |
|             | 2015   | China.      | 5 matched cell lines, 114 cases and 114 controls | 2/5 Breast cancer cell lines and 8.77% (10/114) tumors undergo somatic mutations of the rs6505162 SNP. | 36         |
|             | 2016   | Chile       | 440 cases and 807 controls | rs6505162:C>A (OR = 1.7 [95% CI 1.0–2.0], p = 0.05). | 99         |
|             | 2014   | China       | 7170 case and 8783 controls | rs6505162 no significant association with the risk of breast cancer in any genetic model. | 116        |
|             | 2015   | South Korea | 136 cases and 224 controls | miR-423C>A polymorphism is associated with increased risk of POI. | 115        |
| Lung cancer (LC) | 2016   | China       | 575 case and 608 controls | rs2910164 G allele was associated with lower risk of lung cancer (OR: 0.80), compared with CC genotype (adjusted OR: 0.77) and CA-AA genotype decreased risk (adjusted OR: 0.54). The allele model with OR of 0.75. | 102        |
|             | 2015   | China       | 258 cases and 310 controls | The interaction between rs6505162 gene and environment was not statistically significant. | 111        |
| Hepatocellular carcinoma (HCC) | 2014   | China       | 984 case and 991 controls | rs6505162 had no effect on the risk of HCC. | 119        |
| Advanced gastric cancer (AGC) | 2013   | Aachen      | 674 AGC patients | rs6505162 had no effect on the risk of AGC. | 121        |
| Wilms tumor (WT) | 2018   | China       | 145 cases and 531 controls. | Susceptibility to WT (CA vs. CC: adjusted OR = 0.65, 95% CI = 0.42–0.99, p = 0.047). Compared with CC genotype, CA/AA genotypes decreased risk of WT (adjusted OR = 0.30, 95% CI = 0.14–0.63, p = 0.002) and clinical stage I+II WT (adjusted OR = 0.42, 95% CI = 0.20–0.85, p = 0.017). | 28         |

(Continues)
High miR-423 expression in glioma patients may indicate advanced grade and poor prognosis. The combination of miR-423-5p with other miRNA biomarkers (miR-150-5p and miR-222-3p) can be used to monitor the malignant progression of oral leukoplakia. Overexpression of miR-423-5p has been implicated as a biomarker or therapeutic target of brain metastasis in lung cancer. The combination of miR-423-3p and the three other miRNAs (miR-148b, miR-221 and miR-23b) has proved to be a novel and non-invasive marker for lung cancer detection, with an area under curve (AUC) of 0.885. Therefore, miR-423 is expected to become a therapeutic target and prognostic marker for lung cancer.

MiR-423 plays a similar prognostic role in HCC patients. When miR-423 was used in combination with three other miRNAs (miR-10a, miR-375, and miR-122), the AUC for the diagnosis of HCC was 0.995. The combination of miR-423-3p with miR-151-5p and miR-152-5p is also a clinically effective marker for cervical cancer patients. In patients with stage I–II colorectal cancer, serum miR-423-5p levels were significantly upregulated compared with the levels in healthy controls, whereas in stage III–IV patients, there was no significant increase in serum miR-423-5p levels. Therefore, plasma levels of miR-423-5p can be used as a biomarker for early detection of colorectal cancer. MiR-423-5p also has a similar function and clinical prognostic value in ovarian cancer. The miRNAs in different ethnic breast cancers, as well as specific genetic variations in miRNA genes, may influence the risk of breast cancer. It has been reported that 70.1% of hereditary breast cancers can be distinguished from non-hereditary breast cancer on the basis of miR-423-3p expression. Identification of the 7-miRNA group (including miR-423-5p) has improved the accuracy of diagnosing bladder cancer with an AUC of 0.923, of which urinary miRNAs may have important clinical value in the prediction of recurrence in bladder cancer. Similarly, serum exosome-derived miR-423 may also be a new target for gastric cancer-specific therapeutic interventions.

In summary, clinical studies of miR-423 in human cancer are still in the preliminary stages, and further large-scale evidence-based medical research is needed to confirm the clinical importance of miR-423.
CONCLUSION

In this review, we have introduced published literature on the dysregulation of miR-423 in malignancies and the molecular mechanism of miR-423 mediated carcinogenesis. Expression of miR-423 has been confirmed to be abnormal in various human cancers and has been revealed as a critical factor involved in tumorigenesis. Although clinical applications of miR-423 in cancer are yet to be established, accumulating evidence supports the use of miR-423 as a biomarker in the early diagnosis and prognosis of human cancers in addition to monitoring treatment efficacy.

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The authors claim that they have no competing interests.

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