Journal of Cancer Research and Clinical Oncology (2025) 151:148
https://doi.org/10.1007/s00432-025-06195-w

REVIEW

Clinical implications of miR-195 in cancer: mechanisms, potential applications, and therapeutic strategies

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Received: 4 February 2025 / Accepted: 3 April 2025 / Published online: 22 April 2025

Abstract

This review explores the dual role of miR-195 in cancer, acting as both a tumor suppressor and, in specific contexts, a tumor promoter. It highlights its molecular mechanisms, focusing on key signaling pathways such as Wnt-1/β-catenin, VEGF/VEGFR, and PI3K/AKT/mTOR, as well as its involvement in competitive gene regulation. The clinical potential of miR-195 in cancer screening, diagnosis, prognosis, and therapy is examined, particularly its ability to enhance therapeutic efficacy and reduce recurrence risk when combined with chemotherapy or immunotherapy. Despite these promising aspects, challenges such as precise regulation, efficient delivery systems, and clinical translation remain. Future research should prioritize advancing miR-195's integration into personalized medicine, immunotherapy, and novel delivery technologies, aiming to establish it as a reliable biomarker and therapeutic target for improved cancer care.

Keywords MiR-195 · Oncogenic mechanisms · Tumor suppressor · MiRNA sponges · Personalized medicine · Cancer therapy

The background and introduction of miR-195

In the pursuit of human health and quality of life, we have been committed to addressing the existential threat of malignancies that overshadow human existence. Research suggests that in this century, cancer will become the leading cause of death in most countries worldwide (Bray et al. 2021). Cancer not only poses a significant threat to human health and life but also serves as a litmus test for national healthcare systems (Frick et al. 2023). Currently, cancer treatment modalities primarily include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. MicroRNAs, small non-coding RNAs, have been under investigation for their role in cancer progression since the identification of miRNA loss and low expression in chronic lymphocytic leukemia in 2002 (Calin et al. 2002; He et al. 2020; Hill and Tran 2021; Zhang et al. 2021). Previous studies have highlighted the involvement of miRNAs in nearly all aspects of cancer progression.

The synthesis of mature miRNA begins with the transcription of nuclear miRNA genes by RNA polymerase II, resulting in the production of primary miRNA transcripts (pri-miRNA) (Lee et al. 2004). Pri-miRNA is then cleaved by the RNase III enzyme Drosha and DGCR8 to generate long precursor miRNA (pre-miRNA) (Blaszczyk et al. 2001), with DGCR8 facilitating the precise cleavage of pri-miRNA (Morlando et al. 2008). Subsequently, the pre-miRNA is exported to the cytoplasm with the assistance of Exportin 5 and RanGTP (Bohnsack et al. 2004). The pre-miRNA is further processed by the ribonuclease

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Dicer, forming mature double-stranded miRNA (miRNA-miRNA*) (Feng et al. 2012), which is then unwound into two independent strands: the passenger strand (miRNA*) and the guide strand (miRNA), through an ATP-dependent process (Liu et al. 2018). In most cases, the passenger strand is degraded, while the guide strand interacts with the AGO protein to form the final AGO-miRNA complex, known as the RNA-induced silencing complex (RISC). RISC targets complementary sequences typically located in the 3'untranslated region (3'-UTR) of mRNA, exerting its effects through mRNA degradation or translation inhibition (Bhaskaran and Mohan 2014).

Previous research has indicated that miRNAs not only target mRNAs but also regulate long non-coding RNAs (lncRNAs), pseudogenes, and circular RNAs (circRNAs) (Tay et al. 2014). The primary mechanism of action of miRNAs involves interactions with various competitive endogenous RNA (ceRNA) networks or target genes within cellular pathways. In these pathways, scenarios may arise where a single miRNA targets multiple genes or where multiple miRNAs regulate a single gene or pathway (Diener et al. 2022). Consequently, the advantage of selecting miRNAs as a therapeutic strategy for cancer lies in their ability to target specific molecules, thereby inhibiting the progression of tumor development. This highlights the notion that miRNAs serve as versatile entry points for the treatment of various diseases. Numerous studies have demonstrated that aberrantly expressed miRNAs can function as oncogenic miRNAs (Onco-miRNAs) or tumor-suppressive miRNAs (TS-miRNAs) (Xu et al. 2022). This dynamic interplay emphasizes the complexity of miRNA-mediated regulatory networks in disease pathology and highlights their potential as therapeutic targets for cancer and other diseases.

microRNA-195 (miR-195) is a critical member of the microRNA-15/16/195/424/497 family, which is activated in various diseases, including cancer (He et al. 2011). The pre-miR-195 gene is located on chromosome 17p13.1, spanning from 6,881,953 bp to 6,862,065 bp (Davoodvandi et al. 2023). The predicted stem-loop structure of miR-195, determined using miRBase (http://mirbase.org/), is shown in Fig. 1, with its mature form possessing the sequence 5′-AGC AGCACAAAUAUUGGC-3′ (Dioguardi et al. 2023). Mature miRNA can be cleaved from the 5'and 3'arms of the precursor duplex, yielding the 5p guide strand and the 3p sister passenger strand, respectively (Almeida et al. 2011). miR-195-3p and miR-195-5p represent two mature forms of miR-195 (He et al. 2017). The generation process of miR-195 is depicted in Fig. 2.

Tumor-suppressive mechanisms of miR-195

Current research indicates that miR-195 is significantly downregulated in multiple malignancies, including hepatocellular (Xu et al. 2009), lung (Li et al. 2020a), cervical (Jin et al. 2021), renal (Sun et al. 2016), laryngeal (Shuang et al. 2017), esophageal (Liu et al. 2020a), peritoneal, (Flavin et al. 2009) and diffuse large B-cell lymphomas (Li et al. 2023). This widespread suppression suggests its potential role as a tumor suppressor.

There is also research directly indicating that miR-195 functions as a tumor suppressor gene. Yao et al. (Lu et al. 2022) found that exosomal miR-195 derived from chondrocytes successfully inhibited osteosarcoma (OS) cell proliferation and resistance to apoptosis in vitro and suppressed tumor growth in vivo. Hu et al. (2023) demonstrated that in gastric adenocarcinoma (GAC) cells, miR-195-5p inhibits cell migration, proliferation, and invasion, as well as the epithelial-mesenchymal transition (EMT) process, promoting apoptosis by regulating OTX1. Liu et al. (2020b) concluded that hsa-miR-195-5p is a potential tumor suppressor miRNA in human thyroid cancer (TC).

miR-195 functions as a tumor suppressor, and its overexpression may offer a strategy for inhibiting malignancies. In lung adenocarcinoma (LUAD), Bu et al. (2022) demonstrated that miR-195-5p suppresses tumor growth by targeting TrxR2, while Fu et al. (2023) identified the hsa-miR-195-5p/E2 F7/CEP55 axis as a regulator of LUAD tumor suppression. Niu et al. (2021) further reported that miR-195-5p inhibits FOXK1, promoting apoptosis in non-small cell lung cancer. Similarly, in lung cancer, Long et al.

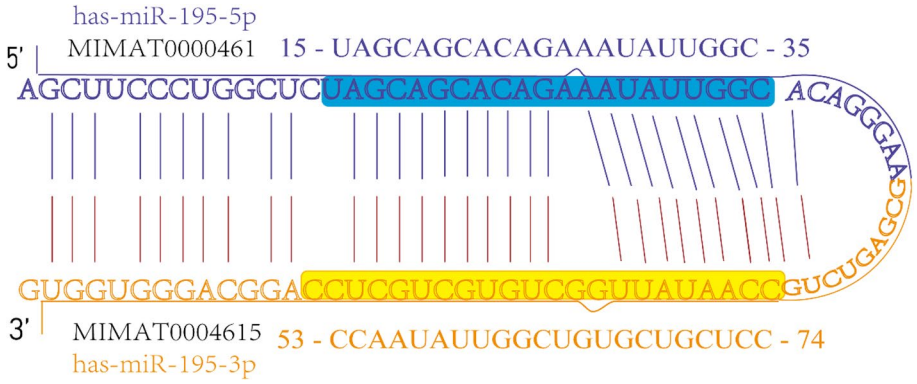

Fig. 1 Schematic representation of the stem-loop structure of miR-195

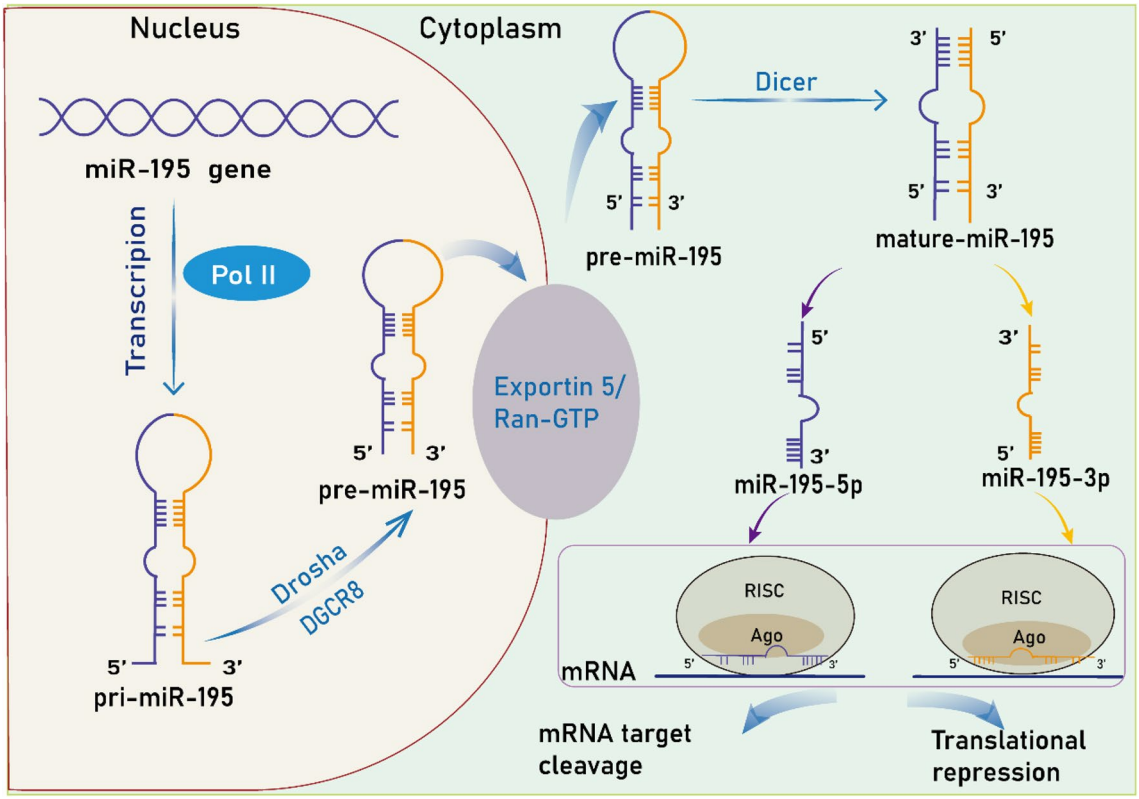

Fig. 2 Biogenesis of miR-195: the nuclear miR-195 gene is transcribed by RNA polymerase II to produce pri-miR-195. Pri-miR-195 is then cleaved by the RNase III enzymes Drosha and DGCR8 to generate a longer precursor intermediate, pre-miR-195. Subsequently, with the assistance of Exportin 5 and RanGTP, pre-miR-195 is exported to the cytoplasm. Thereafter, pre-miR-195 is processed by the endonuclease Dicer to form mature miR-195. The mature miR-195 undergoes an ATP-dependent unwinding process into two independent strands (miR-195-5p and miR-195-3p). Each strand interacts with AGO proteins to form the RNA-induced silencing complex (RISC). RISC then binds to complementary target sequences, typically located in the mRNA 3'untranslated region (3'-UTR), exerting its effects through mRNA cleavage or translational repression

(2020a) and Zhou et al. (2019) confirmed its role in inhibiting proliferation, migration, and invasion.

In cervical cancer, Liu et al. (2023) and Yuan et al. (2020) demonstrated that miR-195-5p suppresses proliferation, migration, and epithelial-mesenchymal transition (EMT) while inducing apoptosis and autophagy. Liu et al. (2020c) further identified YAP1 as a direct target. miR-195 also plays a role in thyroid cancer by regulating telomerase reverse transcriptase (Liu et al. 2021a) and in renal cell carcinoma by inhibiting viability, migration, and invasion (Sun et al. 2016).

Beyond these, miR-195 has been shown to suppress hemangioma (HA) cell proliferation and promote apoptosis via Bcl-2/Bax modulation (Sun et al. 2022), inhibit esophageal cancer cell migration and invasion by downregulating FOSL1 (Shen et al. 2020), and regulate hepatocellular carcinoma (HCC) progression by targeting CDK1 (Zhou et al. 2023a). It also contributes to colorectal cancer suppression by downregulating FRA1 and γ-catenin, limiting proliferation, invasion, and migration (Piccinno et al. 2023a; Huang et al. 2024). In prostate cancer, miR-195 inhibits cell cycle progression and angiogenesis by targeting PRR11 and Fra-1 (Lai et al. 2018; Wu et al. 2015).

Furthermore, Cao et al. (2020) demonstrated that upregulating miR-195 suppresses proliferation and migration in human liposarcoma cells (SW872 and 93 T449), leading to growth inhibition and apoptosis. Likewise, Luo et al. (2024) reported that PM2.5 exposure increases HCG18 expression, which suppresses miR-195, thereby activating autophagy and promoting lung tumorigenesis.

Conversely, downregulation of miR-195 promotes malignant tumor progression. Li et al. (Huang et al. 2024) reported that inhibiting miR-195-5p attenuates its suppressive effects on colorectal cancer cell proliferation, migration, and invasion. Similarly, suppressing miR-195-5p expression in mycosis fungoides has been shown to enhance tumor cell proliferation (Rittig et al. 2021). A summary of the tumor-suppressive effects of miR-195 across various malignancies is presented in Table 1.

Table 1 Mechanisms of miR-195 in Tumor Suppression Across Different Cancers

Human system	Disease	miRNAs	Levels in cancer cell lines compared with normal cell lines	Interactions	Downstream target of miRNA	Effect of miRNAs up-regulation on tumor	Associated phenotypes with dysregulation of miRNA-195	Refs.
Liver	Hepatocellular carcinoma	miR-195	Down	CyclinD1, CDK6,E2 F3	CyclinD1, CDK6,E2 F3	Inhibition	↑miR-195,↓CyclinD1, ↓CDK6,↓E2 F3: ↓G_1/S transition, ↓tumor growth	Xu et al. (2009)
		miR-195-5p	Down	CDK1	CDK1	Inhibition	↑miR-195-5p,↓CDK1: ↓G1/S transition, ↓ cell growth	Zhou et al. (2023a)
		miR-195-5p	Down	PLAG1	PLAG1	Inhibition	↑miR-195-5p, ↓PLAG1: ↑cell ferroptosis	Li et al. (2024a)
Lung	Lung adenocarcinoma	miR-195-5p	Down	TrxR2	TrxR2	Inhibition	↑miR-195-5p, ↓TrxR2: ↓cell migration, proliferation, invasion, ↑apoptosis, ↓tumor growth	Li et al. (2022)
		miR-195-5p	Down	E2 F7/CEP55	E2 F7/CEP55	Inhibition	↑miR-195-5p, ↓E2 F7/CEP55: ↓tumor growth, ↑apoptosis, ↑autophagy	Fu et al. (2023)
		miR-195	Down	apelin	apelin	Inhibition	↑miR-195, ↓apelin: ↓cell proliferation and invasion	Zhou et al. (2019)
		miR-195	Down	ATG14	ATG14	Inhibition	↑miR-195, ↓ATG14: ↑apoptosis	Luo et al. (2024)
	Lung cancer	miR-195-5p	Down	FOXK1	FOXK1	Inhibition	↑miR-195-5p, ↓FOXK1:↓cell migration, invasion, and proliferation	Li et al. (2020a)
	Non-small cell lung cancer	miR-195-5p	Down	FOXK1	FOXK1	Inhibition	↑miR-195-5p, ↓FOXK1: ↑apoptosis	Niu et al. (2021)
Kidney	Clear cell renal cell carcinoma	miR-195	Down	PI3 K/Akt, Raf/MEK/ERK,VEGFR2	VEGFR2	Inhibition	↑miR-195,↓VEGFR2,↓PI3 K/Akt, ↓Raf/MEK/ERK:↓cell viability, migration and invasion, ↑apoptosis	Sun et al. (2016)
Head and neck	Laryngeal squamous cell carcinoma	miR-195	Down	DCUN1D1	DCUN1D1	Inhibition	↑miR-195, ↓DCUN1D1:↓cell proliferation and invasion	Shuang et al. (2017)

Table 1 (continued)

Human system	Disease	miRNAs	Levels in cancer cell lines compared with normal cell lines	Interactions	Downstream target of miRNA	Effect of miRNAs up-regulation on tumor	Associated phenotypes with dysregulation of miRNA-195	Refs.
Esophagus	Esophageal squamous cell carcinoma	miR-195	Down	lncRNA FOXD2-AS1, Akt/mTOR	Akt/mTOR	Inhibition	↓miR-195, ↑lncRNA FOXD2-AS1, ↑Akt/mTOR: ↑cell resistance to cisplatin	Liu et al. (2020a)
	Esophageal cancer	miR-195-5p	Down	lncRNA AGAP2-AS1,FOSL1	FOSL1	Inhibition	↑miR-195-5p, ↓lncRNA AGAP2-AS1, ↓FOSL1: ↓cell proliferation, migration and invasion, ↑apoptosis	Shen et al. (2020)
Bone	Osteosarcoma	miR-195	Down	KIF4 A	KIF4 A	Inhibition	↑miR-195, ↓KIF4 A: ↓cell proliferation,↑apoptosis	Lu et al. (2022)
Gastrointestinal	Gastric adenocarcinoma	miR-195-5p	Down	OTX1	OTX1	Inhibition	↑miR-195-5p, ↓OTX1: ↓cell migration, proliferation, invasion and EMT, ↑apoptosis	Hu et al. (2023)
	Colorectal cancer	miR-195/497	Down	FRA1	FRA1	Inhibition	↑miR-195/497, ↓FRA1: ↓cell migration, proliferation, invasion and EMT	Huang et al. (2024)
		miR-195-5p	Down	JUP	JUP	Inhibition	↑miR-195-5p, ↓JUP: ↓cell viability, proliferation and invasion, ↓tumor growth	Piccinno et al. (2023a)
		miR-195-5p	Down	lncRNA AFAP1-AS1, WISP1	WISP1	Inhibition	↑miR-195-5p, ↓ lncRNA AFAP1-AS1, ↓WISP1: ↓cell proliferation, migration and invasion,	Li et al. (2021a)

Table 1 (continued)

Human system	Disease	miRNAs	Levels in cancer cell lines compared with normal cell lines	Interactions	Downstream target of miRNA	Effect of miRNAs up-regulation on tumor	Associated phenotypes with dysregulation of miRNA-195	Refs.
Reproductive and urinary	Cervical cancer	miR-195-5p	Down	ATG9 A	ATG9 A	Inhibition	↑miR-195-5p, ↓ATG9 A: ↓cell migration, proliferation and EMT, ↑apoptosis, ↑autophagy	Liu et al. (2023)
		miR-195 − 3p	Down	BCDIN3D	BCDIN3D	Inhibition	↑miR-195-3p,↓BCDIN3D:↓cell proliferation	Jin et al. (2021)
		miR-195	Down	lncRNA SNHG1, NEK2	NEK2	Inhibition	↑miR-195-5p, ↓lncRNA SNHG1 ↓NEK2: ↓cell viability, migration and invasion, ↑apoptosis	Ji et al. (2020)
		miR-195-5p	Down	YAP1	YAP1	Inhibition	↑miR-195-5p, ↓YAP1: ↓cell migration, proliferation, invasion and EMT	Liu et al. (2020c)
	Prostate cancer	miR-195	Down	Fra-1	Fra-1	Inhibition	↑miR-195, ↓Fra-1:↓cell migration and invasion	Wu et al. (2015)
	Prostate cancer	miR-195	Down	PRR11	PRR11	Inhibition	↑miR-195, ↓PRR11:↓cell proliferation, cell cycle progression and HUVEC tube formation	Lai et al. (2018)
Soft tissue	Liposarcoma	miR-195	Down	OSBP	OSBP	Inhibition	↑miR-195, ↓OSBP: ↓cell proliferation and migration ↑ apoptosis	Cao et al. (2020)
	Hemangioma	miR-195-5p	Down	SKI	SKI	Inhibition	↑miR-195-5p, ↓SKI: ↓cell viability, colony formation and proliferation, ↑apoptosis	Sun et al. (2022)
Thyroid	Thyroid cancer	miR-195-5p	Down	TERT	TERT	Inhibition	↑miR-195-5p, ↓TERT: ↓cell proliferation and invasion, ↑apoptosis,	Liu et al. (2021a)

Oncogenic mechanisms of miR-195

Aberrant miRNA expression in certain malignancies does not always deter cancer onset; instead, it can sometimes play a pro-oncogenic role, driving tumor progression. miR-195 is no exception. Plasma levels of miR-195 are significantly higher in chronic lymphocytic leukemia (CLL) patients compared to healthy individuals (Bagheri et al. 2021). A study comparing differential plasma miRNA expression between patients with head and neck squamous cell carcinoma (HNSCC) and healthy individuals revealed high plasma expression of miR-195-5p (Summerer et al. 2015).

Additionally, miR-195 expression decreases upon treatment with cyclosporin A (CsA), suggesting its potential oncogenic role, as its downregulation in human glioma cells triggers glioblastoma formation (Yilaz Susluer et al. 2015). Research indicates that miR-195 may function as an oncogene in CLL, promoting the proliferation and survival of malignant CLLB cells while inhibiting apoptosis by directly targeting DLEU7 mRNA (Bagheri et al. 2021). Furthermore, overexpressing miR-195 in SK-Mel-28 melanoma cells not only enhances melanoma cell proliferation but also increases migration and invasion (Bhattacharya et al. 2013).

The role of miR-195 in promoting tumor progression across various malignancies is summarized in Fig. 3.

MiR-195 in regulating signaling pathways of tumor progression

Wnt-1/β-Catenin signaling pathway

The Wnt-1/β-catenin signaling pathway is a highly conserved pathway that regulates cell proliferation, differentiation, apoptosis, stem cell self-renewal, tissue homeostasis, and wound healing. Dysregulation of this pathway is implicated in various stages of tumor development (Zhou et al. 2022). Zhu et al. (2022) demonstrated that miR-195-5p overexpression directly targets FOS-like antigen-1 and modulates the Wnt/β-catenin signaling pathway, thereby suppressing the proliferation, invasion, and migration of gallbladder cancer (GBC) cells. Wu et al. (2019) suggested that the LncRNA BANCR/miR-195-5p axis may regulate pancreatic cancer cell proliferation and metastasis via the Wnt/β-catenin pathway. In colorectal cancer (CRC), miR-195-5p has been shown to indirectly regulate desmoglein and other key components of this pathway (Piccinno et al. 2023b). Additionally, Wang et al. (2023) reported that Toosendanin (TSN) reduces cisplatin resistance in ovarian cancer by modulating the miR-195/ERK/β-catenin pathway.

VEGF/VEGFR signaling pathway

The VEGF/VEGFR signaling pathway plays a pivotal role in angiogenesis, which is essential for tumor growth (Liu et al. 2021b). Activation of this pathway within the tumor microenvironment enhances tumor cell migratory ability, immune evasion, invasiveness, and vascular density (Mabeta and Steenkamp 2022). Wang et al. (2020) demonstrated that lncRNA DLX6-AS1 exerts oncogenic effects in bladder cancer via the miR-195-5p-mediated VEGFA/Ras/Raf/MEK/ERK pathway. Additionally, miR-195 has been shown to induce apoptosis in clear cell renal cell carcinoma by targeting VEGFR2 through the PI3 K/AKT and Raf/MEK/ERK signaling pathways (Sun et al. 2016).

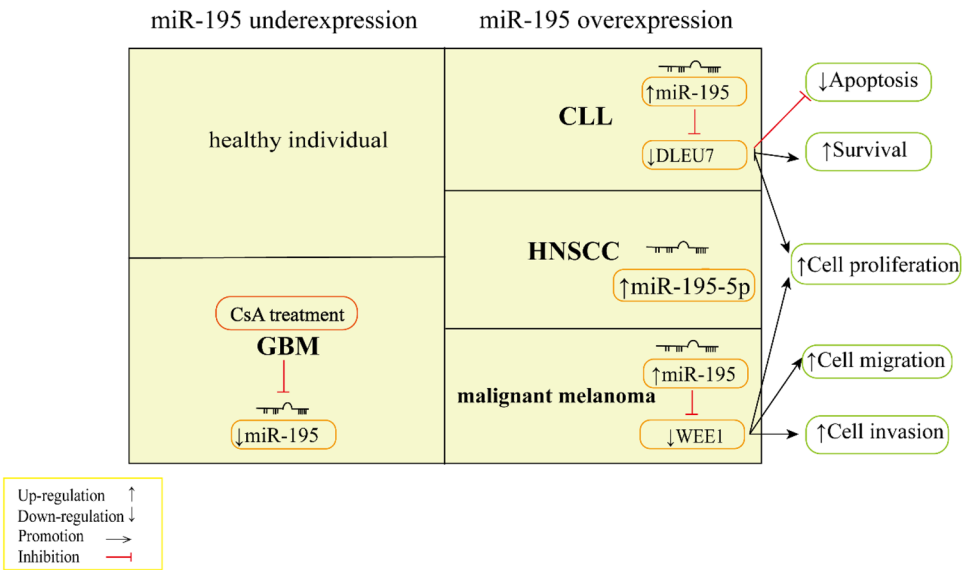

Fig. 3 The mechanism by which miR-195 promotes tumor progression

PI3 K/AKT/mTOR signaling pathway

The phosphatidylinositol 3-kinase (PI3 K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway plays a crucial role in tumor progression (Wang et al. 2019). Given its stimulatory effect in drug-resistant (Liu et al. 2020a) malignancies, the AKT/mTOR axis has been implicated in cisplatin resistance. It has been reported that the long non-coding RNA FOXD2-AS1 promotes cisplatin resistance in esophageal squamous cell carcinoma via the miR-195/AKT/mTOR axis. Moreover, miR-497/195 synergistically suppresses five key regulators of PI3 K/AKT signaling—MAP2 K1, AKT3, BCL2, RAF1, and CCND1—thereby inhibiting PI3 K/AKT signal transduction (Tian et al. 2023). Kong et al. (Kong et al. 2018) found that miR-195 targets FGFR1 and FGF2, leading to the inhibition of PI3 K/AKT and MAPK/ERK pathways, ultimately suppressing endometrial cancer. Wang et al. (2019) further observed that miR-195 may inhibit colorectal cancer progression by modulating the PI3 K/AKT pathway.

Competitive binding in miR-195 regulatory networks

In gene regulatory networks, there is an intriguing mode of RNA action. Transcriptional pseudogenes, long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and mRNAs can act as natural miRNA sponges. These transcripts competitively bind to miRNAs, isolating them from their targets, thus forming naturally occurring endogenous miRNA sponges, known as competitive endogenous RNAs (ceRNAs)(Alkan and Akgül 2022). When miR-195 is targeted by competitive endogenous RNAs and sequestered by these molecules, the defensive barrier collapses, allowing malignant tumors to continue their progression.

For example, lncRNAs regulate miRNAs by competitively binding to target sites on mRNAs encoding proteins. Studies have shown that lncRNA TINCR acts as a ceRNA and competitively sequesters miR-195-3p, alleviating the suppressive effect of miR-195-3p on ST6GAL1, enhancing the NF-κB pathway, and promoting both in vitro and in vivo progression of hepatocellular carcinoma (HCC) cells as well as oxaliplatin resistance(Mei et al. 2022). Xu et al. (2021) reported that Hsa_circ_0060927 acts as a potential key ceRNA, competitively binding to downstream miR-195-5p and upregulating TRIM14 to promote the malignant transformation of oral leukoplakia (OLK) into oral squamous cell carcinoma. Zhu et al. (2021) demonstrated that hsa_circ_0013401 accelerates the growth and metastasis of neuroblastoma cells by releasing PAK2 via miR-195 sponging, thereby preventing apoptosis and autophagy of neuroblastoma cells. Li et al. (2024b) found that hsa_circ_0021205 acts as a sponge for miR-195-5p to regulate the expression of hormone-sensitive lipase (HSL), further promoting lipolysis and driving the malignant progression of glioblastoma. Xiao et al. (2021) found that Circ_CLIP2 inhibits HMGB3 expression by directly sponging miR-195-5p, thereby promoting glioma progression.

Wu's study suggested that lncRNA RUNX1-IT1 may promote the proliferation of glioblastoma cells by competitively binding to and sequestering miR-195, leading to the upregulation of cyclin D1(Wu 2023). Yang et al. (2021) found that circ_001422 upregulates FGF2 expression by sponging miR-195-5p, thereby triggering the activation of the PI3 K/Akt pathway and accelerating osteosarcoma progression through mechanisms such as the inhibition of apoptosis and the promotion of cell proliferation, migration, and invasion. Li et al. (2021b) found that LINC00473 induces cell proliferation, cell cycle progression, and epithelial-mesenchymal transition (EMT) processes by acting as a ceRNA for miR-195 in colorectal cancer.

Chen et al. (2021) discovered that CircWHSC1 regulates the FASN/AMPK/mTOR axis by sponging miR-195-5p, promoting breast cancer progression. Zeng et al. (2021) demonstrated that CircPVT1 promotes VEGFA expression by sponging miR-195, thereby facilitating the malignant progression of papillary thyroid carcinoma (PTC). Xi et al. (2021) found that Hsa_circ_0060937 accelerates the progression of non-small cell lung cancer (NSCLC) by sequestering miR-195-5p and upregulating HMGB3.

Ni et al. (2023) identified LINC00324 as a sponge for miR-195-5p, regulating the proliferation, migration, and invasion of cervical cancer cells, thereby influencing cervical cancer progression. Xiong et al. (2023) reported that lncRNA CERS6-AS1 promotes the development of cervical cancer by acting as a sponge for miR-195-5p. Conversely, Qi et al. (2024) found that inhibiting miR-195-5p counteracted the inhibitory effects of LINC00943 silencing on the biological functions of HCC cells.

In summary, miR-195 plays a crucial role in gene regulatory networks, influencing tumor initiation and progression through intricate competitive binding mechanisms. As illustrated in Fig. 4, miR-195 impacts tumor development across various malignancies by modulating gene regulatory networks through these competitive binding mechanisms.

Clinical significance of miR-195 in tumor screening, diagnosis, and prognosis

It is well known that early detection of malignant tumors significantly improves patient survival rates through effective treatment. Therefore, identifying biomarkers that can effectively indicate malignant tumors is of great significance for clinical treatment. MicroRNAs (miRNAs) in human

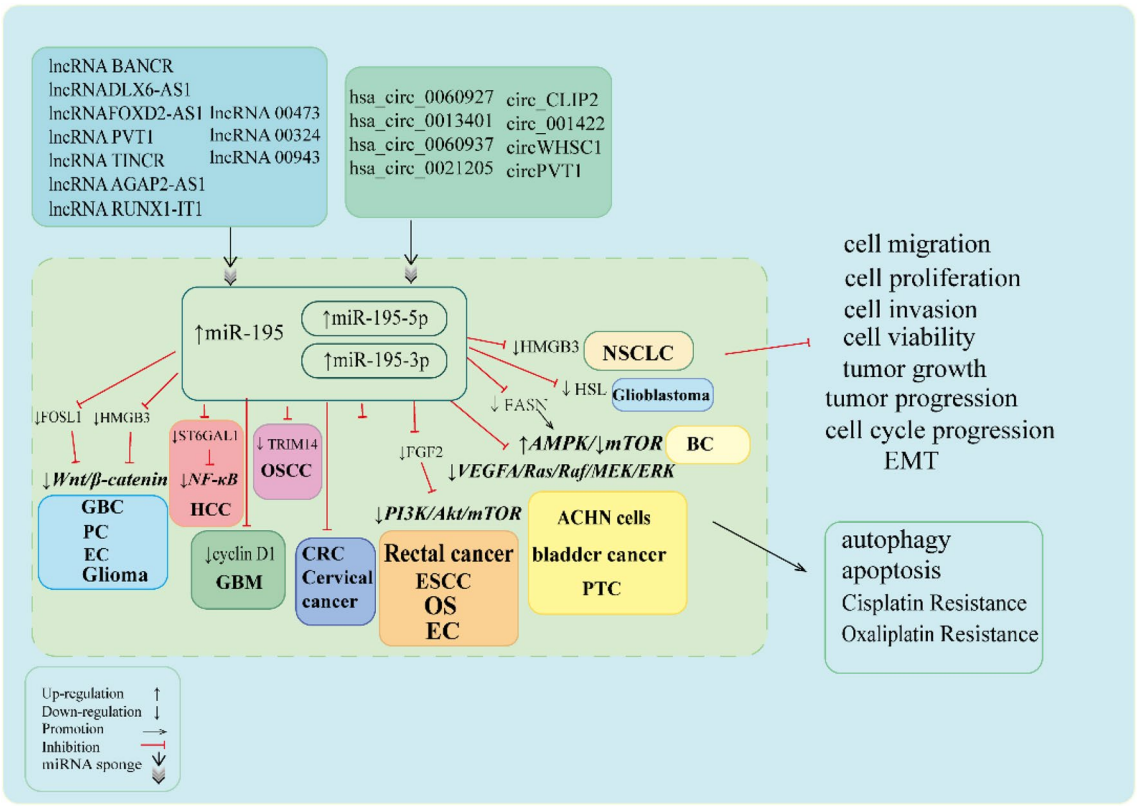

Fig. 4 miR-195 influences tumor initiation and progression in different malignancies through competitive binding mechanisms in gene regulatory networks

body fluids exhibit high stability, and circulating miRNAs are considered promising biomarkers for the early detection, diagnosis, and prognosis of various malignancies (Ho et al. 2022).

Research has shown that miR-195 has significant potential for screening, diagnosis, and prognostic evaluation in various tumors such as renal cell carcinoma (Soon et al. 2009), colorectal cancer (Bayat et al. 2022), lung cancer (Li et al. 2020b; Lao et al. 2022; Zhou et al. 2023b), acute myeloid leukemia (Cui et al. 2021), breast cancer(Zhao et al. 2014; Tokumaru et al. 2021), gastric cancer (Song et al. 2020), and prostate cancer (Cai et al. 2015). For instance, Wang et al. (Huang et al. 2020) found that miR-195-5p could serve as a potential biomarker for cervical cancer patients undergoing venous thromboembolism therapy. Studies have indicated that miR-195 is significantly downregulated in adrenocortical carcinoma and has been identified as an unfavorable prognostic factor (Soon et al. 2009). These findings suggest that miR-195-5p may serve as a molecular biomarker for the early detection and treatment of renal cell carcinoma.

Research has also shown that low levels of miR-195-5p are significantly correlated with TNM staging, lymph node metastasis, and tumor differentiation in colorectal cancer patients (all p-values <0.05), and low expression of miR-195-5p is associated with poor OS (Bayat et al. 2022). Lao et al. (2022) found a significant correlation between miR-195-3p expression and immune infiltration, with miR-195-3p expression significantly lower in lung adenocarcinoma (LUAD) tissues compared to normal lung tissues. Moreover, low expression of miR-195-3p in LUAD patients is associated with poorer OS. Zhou et al. (2023b) suggested that exosomal miR-195-5p represents a promising novel diagnostic biomarker for lung cancer. Li et al. (2020b) proposed that hsa-miR-195-5p could serve as a biomarker for the early detection of lung cancer.

Cui et al. (2021) found that high expression of miR-195 could prolong the prognosis of cytogenetically normal acute myeloid leukemia (AML) patients. Research has indicated that tumors with low expression of miR-195 exhibit high proliferation of estrogen receptor (ER)-positive breast cancer cells, enhanced glycolysis, and lower survival rates (Tokumaru et al. 2021). Zhao et al. (2014) demonstrated that serum microRNA-195 is downregulated in breast cancer and could be a promising tumor marker for early breast cancer diagnosis and population-wide screening. A study analyzing plasma miRNAs in breast cancer patients found that the ROC curve analysis of miR-195 (AUC = 0.672, 95% CI: 0.553–0.792, p = 0.004)

demonstrated high diagnostic accuracy in distinguishing BC patients from healthy women. Additionally, miR-195 exhibited a high sensitivity of 77.8% (Miranda et al. 2024). Song et al. (2020) found that serum miR-195-5p was decreased in gastric cancer patients, suggesting that miR-195-5p may serve as an effective biomarker for the diagnosis and prognosis of gastric cancer patients. Cai et al. (2015) identified through survival analysis that miR-195 serves as an independent prognostic factor for biochemical recurrence-free survival in prostate cancer (PCa) patients ($P = 0.022$).

In addition, miR-195 can be utilized in combination with other molecular markers to enhance the accuracy and practicality of diagnostic models. For example, Yang et al. (2019) noted that the combined detection of miR-1202 and miR-195 holds clinical value in the early diagnosis of cervical cancer. Jing et al. (2024) assessed the diagnostic potential of miR-195-5p, miR-195-3p, and three other miRNAs for BC through ROC analysis. They found that the level of miR-195-3p was significantly higher in BC patients compared to benign controls. All five miRNAs exhibited strong diagnostic potential, with AUC values greater than 0.8. Based on these findings, a comprehensive model incorporating these five miRNAs was developed to improve diagnostic accuracy, offering hope for early, non-invasive, and highly accurate diagnosis of BC. Shi et al. (2024) analyzed mRNA and miRNA expression profiles of BC patients from The Cancer Genome Atlas (TCGA) and identified six glycolysis-related miRNAs, including hsa-miR-195, that were associated with the prognosis of BC patients. They concluded that these miRNAs could serve as effective prognostic indicators of BC.

In the future, as research advances and technology progresses, miR-195 is expected to play an even greater role in cancer early detection, therapeutic evaluation, and personalized medicine. The role of miR-195 as a tumor biomarker in various malignancies is detailed in Fig. 5.

Multidimensional challenges of miR-195 in cancer research and clinical translation

The dual role of miR-195 in oncogenesis and the complexity of its regulatory networks

Despite remarkable progress in oncology research, the multifaceted biological functions of miR-195 continue to pose challenges for both basic and clinical studies. miR-195 exhibits broad tumor-suppressive properties; however, under certain conditions, it may also promote tumor progression. This dual role makes its precise regulation in cancer therapy a critical challenge. As summarized earlier, miR-195 primarily acts as a tumor suppressor in 15 distinct solid tumor types, including hepatocellular carcinoma and lung cancer. However, in chronic lymphocytic leukemia (CLL) patient plasma, glioblastoma, and SK-Mel-28 melanoma cells, miR-195 may promote tumor cell invasion. Additionally, research findings in head and neck squamous cell carcinoma (HNSCC) are somewhat contradictory. For instance, elevated plasma levels of miR-195-5p have been observed

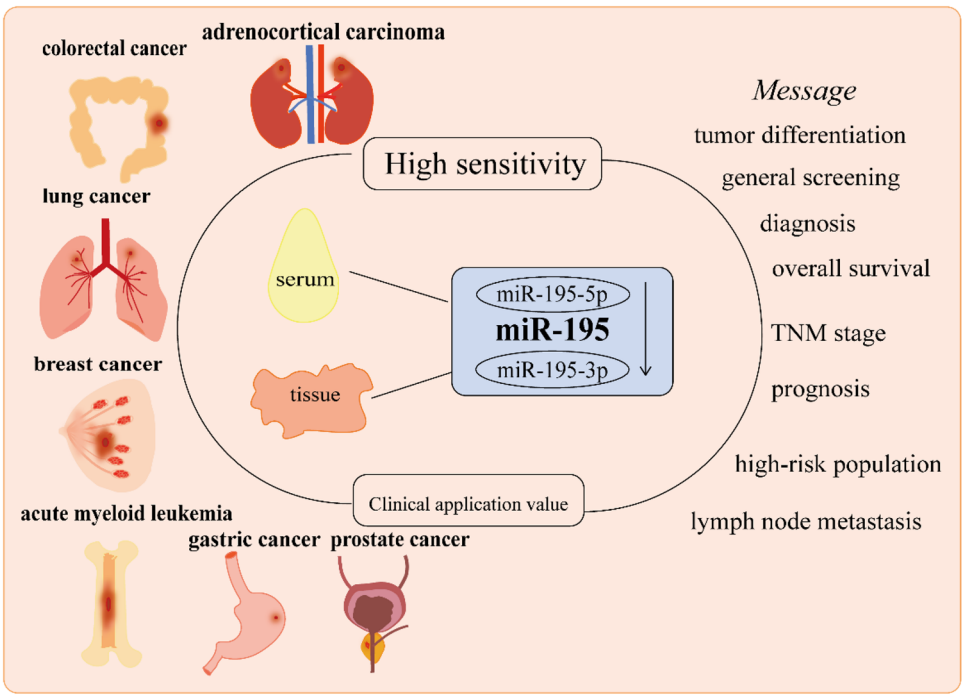

Fig. 5 miR-195: a versatile biomarker in cancer diagnosis and prognosis

in HNSCC patients. However, a study by Wu et al. have demonstrated that dihydroartemisinin (DHA) suppresses the migration and invasion of HNSCC cells by modulating miR-195-5p expression (Wu et al. 2024). This phenomenon suggests that the function of miR-195 may be influenced by specific signals within the tumor microenvironment. Therefore, a key challenge for its clinical application is determining how to precisely assess the mechanism of miR-195 by integrating tumor gene expression profiles with microenvironmental characteristics.

During tumor initiation and progression, miR-195 exerts its biological effects by regulating multiple key signaling pathways, including Wnt-1/β-catenin, VEGF/VEGFR, and PI3 K/AKT/mTOR. These pathways are intricately interconnected, forming a complex molecular network that may lead to unexpected biological outcomes, thereby complicating the therapeutic targeting of miR-195. Furthermore, the function of miR-195 is not isolated but is influenced by interactions with various molecules. It not only exerts its effects by directly targeting multiple tumor-related genes but also interacts synergistically or antagonistically with other miRNAs, transcription factors, and proteins to co-regulate the expression of cancer-associated genes. This intricate gene regulatory network renders the function of miR-195 highly context-dependent, potentially resulting in distinct or even contradictory biological effects across different cancer types and biological conditions. Future research should further explore the role of miR-195 within complex gene regulatory networks, particularly its cooperative interactions with other molecules, to enhance our understanding of its biological functions and clinical application potential.

Barriers to the clinical translation of miR-195

Currently, miRNA-based cancer therapies primarily utilize viral or non-viral vectors for gene delivery, alongside exosome-mediated delivery (Holjencin and Jakymiw 2022). While viral vectors offer high efficiency, their immunogenicity and the risk of genomic integration pose significant safety concerns. Conversely, non-viral vectors, particularly lipid-based drug delivery systems, have demonstrated poor clinical efficacy and severe adverse effects (Wang 2024; Lu et al. 2018). Although nanocarrier-based delivery systems can enhance the stability, specificity, and delivery efficiency of miRNA drugs, their effectiveness and safety require optimization for each specific application due to individual variations (Wang 2024).

Exosome-mediated miRNA delivery is considered safe, highly biocompatible, and capable of crossing the blood–brain barrier (BBB) while inducing immune tolerance in vivo. However, major challenges remain, including the difficulty of producing large quantities of highly purified exosomes, their rapid clearance from the bloodstream, and their accumulation in vital organs (Lu et al. 2018; Arghiani and Shah 2021). Recent studies have shown that the antitumor activity of miR-195-5p can be transmitted to bystander cells via extracellular vesicles (EVs), thereby enhancing melanoma responses to targeted therapy (Santos et al. 2023). Additionally, research has demonstrated that encapsulating a combination of three miRNAs (miR-195-5p/miR-520a/miR-630) in lipid nanoparticles effectively prevents lung metastases in a spontaneous metastasis mouse model. This miRNA mixture holds promise as an anti-metastatic therapy by inhibiting tumor cell dedifferentiation, a process that occurs at secondary tumor sites and drives the transition from micrometastases to macrometastases (Nevskaya et al. 2024).

Thus, despite the significant potential of miRNA-based cancer therapies, their clinical application remains hindered by numerous technical and safety challenges. To facilitate the clinical translation of miR-195, future research must focus on overcoming technical bottlenecks through the development of highly efficient and targeted delivery systems.

Future research directions of miR-195

Future research on miR-195 can be explored from several perspectives.

First, miR-195 holds promise for breakthroughs in precision medicine. Studies have suggested that restoring the expression of tumor-suppressive miRNAs may serve as an effective cancer therapy (Li et al. 2024c). As a crucial tool in cancer diagnosis and treatment, miR-195 can target specific tumor pathways to provide precise therapeutic interventions for various cancers. For instance, miR-195-5p has demonstrated potential as an antiproliferative, antimigratory, and anti-invasive therapy for oral squamous cell carcinoma (OSCC) (Malekjafarian et al. 2024). Wu et al. (2024) have found that dihydroartemisinin (DHA) inhibits the invasion and migration of head and neck squamous cell carcinoma (HNSCC) by modulating miR-195-5p expression. Similarly, Lang et al. (Sheng et al. 2021) have reported that Atractylenolide III suppresses human hepatocellular carcinoma (HCC) cell growth and induces apoptosis by upregulating miR-195-5p and downregulating FGFR1 expression.

Moreover, Wu et al. (2021) have demonstrated that maojianmycin alleviates triple-negative breast cancer (TNBC) by inhibiting the lncRNA AFAP1-AS1–miR-195/miR-545 axis, suggesting that combining molecular targets with traditional Chinese medicine could significantly enhance TNBC treatment efficacy. Xue et al. (2022) have found that Astragalus suppresses cervical cancer cell proliferation, migration, and invasion via the miR-195-5p/LOXL2 axis. Additionally, research has highlighted the clinical potential of miR-195-5p

in regulating adherens junctions and CRC progression (Piccinno et al. 2024).

Second, miR-195, when combined with existing therapies such as chemotherapy, radiotherapy, or immunotherapy, may enhance treatment efficacy and reduce the risk of tumor recurrence.

For instance, Gao et al. (2022) have found that propofol enhances the cytotoxic effect of cisplatin on hepatocellular carcinoma cells by upregulating miR-195-5p. Additionally, research suggests that miR-195-5p may serve as a biomarker for prognosis and early detection of trastuzumab resistance in HER2-positive breast cancer patients (Rezaei et al. 2023). In sorafenib-treated hepatocellular carcinoma, Li et al. (2024a) have discovered that the regulation of the PVT1/miR-195-5p axis determines the impact of PLAG1 on ferroptosis inhibition. Similarly, Wu et al. (2024) have reported that miR-195-5p enhances DNA damage in LUAD (lung adenocarcinoma) cells by suppressing E2 F7, thereby increasing their sensitivity to cisplatin.

Moreover, Luo et al. (2023) have demonstrated that HOTAIR regulates ABCG2-induced oxaliplatin resistance in gastric cancer through miR-195-5p signaling. Chai et al. (2024) have found that circ_0081069, transported via exosomes, binds to miR-195-5p to induce SPIN1 expression, thereby reducing the radiosensitivity of esophageal squamous cell carcinoma. Research has also shown that the combined use of the antioxidant resveratrol (RSV) and tamoxifen (TAM) increases the expression of tumor-suppressive miRNAs, including miR-195-3p, enhancing the sensitivity of drug-resistant BC cells to TAM (Deljavan Ghodrati and Comoglu 2024).

Furthermore, Yu et al. (2018) have reported that miR-195 synergizes with microtubule-targeting agents (MTAs) to inhibit the growth of NSCLC cells in vitro. Increased miR-195 expression sensitizes NSCLC cells to MTAs, whereas miR-195 inhibition confers resistance to MTAs. Another study indicated that restoring seven miRNAs, including miR-195-5p, suppresses PD-L1 expression in tumors, transforming an immunosuppressive tumor microenvironment into a pro-inflammatory one. This process inhibits tumor proliferation and migration, enhances chemotherapy sensitivity, stimulates tumor apoptosis, induces cell cycle arrest, suppresses tumor clonogenicity, and regulates various oncogenic signaling pathways in triple-negative breast cancer (TNBC) cells. Single-cell sequencing-guided biomimetic delivery of these PD-L1-suppressing miRNAs may reduce toxicity associated with conventional approaches, improve the specificity of miRNA delivery, enhance therapeutic efficacy, and provide personalized cancer treatment for affected patients (Shadbad et al. 2021).

Additionally, Tao et al. (2018) have found that the miR-195/−16 family enhances radiotherapy by blocking the PD-L1 immune checkpoint and activating T cells in the tumor microenvironment. Ma et al. (2022) have developed nano-bubbles (NBs) co-loaded with miR-195 and chlorin e6 (Ce6) and used NBs as carriers to deliver miR-195 and Ce6 to tumor models in mice. The results demonstrated that sonodynamic therapy (SDT)-induced immunogenic cell death (ICD) in tumor cells, combined with miR-195-mediated PD-1/PD-L1 immune checkpoint blockade, triggered a stronger antitumor immune response. These findings provide new strategies for miR-195-based combination immunotherapy.

Third, mir-195 holds great promise for applications in personalized medicine. by assessing mir-195 expression levels in patients through liquid biopsy techniques, personalized treatment plans can be designed. moreover, integrating artificial intelligence and bioinformatics analyses to predict mir-195 target genes and potential functions may provide additional data support for clinical practice.

For example, Cui et al. (2024) have isolated plasma miRNAs from peripheral blood samples of healthy individuals, patients diagnosed with papillary thyroid carcinoma (PTC), and patients with benign thyroid nodules. an illumina novaseq 6000 platform was used to establish miRNA expression profiles. using a random forest algorithm, a 7-miRNA panel was developed in plasma, demonstrating significant performance in distinguishing PTC from healthy or benign groups. among them, plasma hsa-miR-195-5p showed potential for further study in the diagnosis of PTC in asian populations.

Another study extracted cell-free RNA and exosomal RNA from preoperative serum and performed quantitative reverse transcription polymerase chain reaction (qRT-PCR) on a set of miRNAs. The results indicated that miR-195, along with three other miRNAs, exhibited strong capability in detecting lymph node metastasis (LNM) within both the exosomal and cell-free components. This novel exosomal miRNA-based liquid biopsy feature can reliably identify patients with T1 colorectal cancer (CRC) at risk of LNM before surgery (Miyazaki et al. 2023).

A separate study utilized next-generation sequencing and three online bioinformatics prediction tools to identify a tumor suppressor gene miRNA signature based on lysine histidine phosphatase inorganic pyrophosphatase (LHPP). Results confirmed that miR-195-5p, along with five other miRNAs, was significantly upregulated in early- and mid-stage esophageal squamous cell carcinoma (ESCC) plasma samples ($P < 0.05$). an ESCC prediction model was established, which demonstrated high discriminative value in an external validation cohort (sensitivity/specificity: 84.4%/93.3%). this model holds potential for the early and mid-stage diagnosis of ESCC (Zhao et al. 2023).

Finally, high-throughput screening and functional validation are critical directions for miR-195 research. Developing new high-throughput screening platforms to systematically

evaluate all potential target genes of miR-195 and their biological functions will aid in comprehensively understanding its role in different tumor types. Additionally, the application of single-cell RNA sequencing (scRNA-seq) technology will reveal the specific roles of miR-195 in different tumor cell populations, providing a theoretical basis for optimizing therapeutic strategies.

For instance, Wang et al. (2024) used weighted gene co-expression network analysis (WGCNA) combined with a competing endogenous RNA (ceRNA) network to investigate potential hub genes and regulatory pathways associated with the occurrence and development of bladder transitional cell carcinoma (BTCC) based on the TCGA dataset. They identified that all elements within the AC112721.1/LINC00473/AC128709.1-has-miR-195-RECK axis were simultaneously correlated with overall survival, potentially offering new therapeutic insights for BTCC.

Another study employed a PCR array containing primers for 84 miRNAs related to genitourinary system cancers to analyze formalin-fixed, paraffin-embedded (FFPE) samples from four cases of diffuse hyperplastic peribronchial nephritis (DHPLN) and adjacent healthy tissues. comparisons were made between miRNA expression in DHPLN and available nephroblastoma (WT) data from the dbDEMC database. Nine miRNAs, including miR-195-5p, showed potential as biomarkers for distinguishing WT from DHPLN in cases where traditional differential diagnosis remains uncertain (Csók et al. 2023).

These findings underscore that miR-195 is not only of significant importance in fundamental research but also exhibits great potential in clinical diagnosis and treatment. Machine learning-based big data analysis can help researchers accurately predict miR-195 target gene networks, uncover its biomarker potential, and optimize individualized treatment strategies. Ultimately, miR-195 is expected to become a powerful tool for early cancer diagnosis and treatment, further advancing the field of personalized medicine.

Conclusion

In summary, miR-195, as a critical cancer-related miRNA, exhibits significant potential in antitumor therapy, drug resistance reversal, and immune regulation. Although current research still faces numerous challenges, the continuous optimization of precise regulatory strategies, advancements in delivery systems, integration with immunotherapy, and the deep application of artificial intelligence and bioinformatics are expected to progressively unveil the full potential of miR-195 in cancer treatment, ultimately facilitating its clinical translation.

Conquering cancer remains a formidable challenge, and miR-195 may serve as a crucial breakthrough in this battle. Together, we stride toward a new era of precision cancer therapy, eagerly anticipating the day when this vision becomes a reality.

Author contributions Writing—original draft preparation, visualization, S.X.; formal analysis, L.H.; software, Y.C.; investigation, T.L.; validation, L.T.; methodology,Y.W.; funding acquisition, Y.H.; project administration, X.S. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Funding This work was supported in part by the National Natural Science Foundation of China (82305329 for L.H., 82302979 for L.T), the National Natural Science Foundation of Hunan Province (2023 JJ30449 for Y.C.H., 2023 JJ40500 for L.H and 2023 JJ40488 for L.T),Hunan Provincial Health High-Level Talent Scientific Research Project (grant number: R2023111 for Y.C.H),the National Natural Science Foundation of Changsha City (kq2208206 for L.H), the Project of Hunan Provincial Department of Education (23 A0298 for Y.C.H), Chinese Academy of Engineering Academician Liang Liu's Workstation of Hunan University of Chinese Medicine (22YS001 for Y.C.H), First-class Discipline Construction Project of Hunan University of Chinese Medicine (22 JBZ011 for Y.C.H), and University level project of Hunan University of Chinese Medicine (2022YYZK010 for L.H),Project of Hunan Administration of traditional Chinese Medicine (C2023004 for Y.H.W), the Project of Hunan Provincial Health Commission (D202307018448 for Y.H.W, D202207015049 for L.T).

Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Informed consent Not applicable.

Institutional review board Not applicable.

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