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REVIEW ARTICLE

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MiR-145 in cancer therapy resistance and sensitivity: A comprehensive review

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Abstract

MircoRNA (miRNA) are a group of small, non–coding, regulatory RNA with an average length of approximately 22 nucleotides, which mostly modulate gene expression post–transcriptionally through complementary binding to the 3′-untranslated region (3′-UTR) of multiple target genes. Emerging evidence has shown that miRNA are frequently dysregulated in a variety of human malignancies. Among them, microRNA-145 (miR-145) has been increasingly identified as a critical suppressor of carcinogenesis and therapeutic resistance. Resistance to tumor therapy is a challenge in cancer treatment due to the daunting range of resistance mechanisms. We reviewed the status quo of recent advancements in the knowledge of the functional role of miR-145 in therapeutic resistance and the tumor microenvironment. It may serve as an innovative biomarker for therapeutic response and cancer prognosis.

KEYWORDS
biomarker, cancer, MiR-145, therapeutic resistance, Therapeutic sensitivity

1 | INTRODUCTION

According to cancer statistics in 2020, the global cancer and mortality incidence were approximately 1.8 million and 0.6 million in the United States, respectively.[1] Metastasis and therapeutic resistance are the leading causes of death in cancer patients. Nevertheless, the mechanisms driving poor responses to anticancer treatments remain to be clarified. Therefore, there is an urgent need for elucidating the underlying and intrinsic molecular mechanisms of resistance and for investigating new and effective therapeutic approaches.

MircoRNA (miRNA) are a group of small endogenous non–coding RNA containing approximately 18-25 nucleotides, which negatively modulate gene expression through interfering with message RNA (mRNA) abundance and transcriptional efficiency.[2] Extensive miRNA research has revealed that they play a critical role in a wide range of cancers, whose deletion, amplification or aberrant expression

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may affect a series of developmental processes by modulating their downstream targeting mRNA expression post–transcriptionally. Among them, microRNA-145 (miR-145) is highly expressed in numerous malignancies and plays a profound role in cancer initiation and therapeutic resistance. In recent five years, accumulating research has focused on the molecular mechanisms of miR-145 mediating the radioresistance and chemoresistance of cancer cells. Researchers are currently attempting to explore the target genes of miR-145 and their signaling pathways involved in altering therapeutic response, which is significant for the development of miRNA-related therapies. Strikingly, various research has disclosed that miR-145 acts in reversion of therapeutic resistance in multiple tumors, including lung cancer,[3-6] esophageal squamous cell carcinoma (ESCC),[7-9] ovarian carcinoma,[10,11] glioma,[12,13] hepatocellular carcinoma (HCC),[14-16] breast cancer,[17] colorectal cancer (CRC) [18-21] prostate cancer,[22,23] bladder cancer,[24] gastric cancer (GC),[25,26] pancreatic adenocarcinoma[27] and cervical cancer.[28,29]

In this review, we summarize the molecular mechanisms and potential pathways involved in the regulation of miR-145, simultaneously focusing on the roles of miR-145 in modulating therapeutic resistance, especially the nature of their intrinsic links across diverse cancers. In addition to its diagnostic or prognostic value, miR-145 can serve as a predictor of chemotherapeutic response.

2 | MIR-145 AND CANCER

Emerging data have indicated that circulating miRNA are diagnostic biomarkers for cancer, dysregulation of which is observed to play a pivotal role in oncogenesis in various cancers.[30,31] New therapies exploited based on an in-depth understanding of the underlying molecular events in tumor biology are currently high priorities. Numerous recent studies have identified innovative and surrogate miRNA-based biomarkers with predictive or therapeutic potential to reduce patient mortality.[32] miR-145 functions in cancers by regulating its downstream molecules, or being regulated by its upstream RNA molecules, such as long noncoding RNA (lncRNA) and circular RNA (circRNA), both of which have been characterized as "miRNA sponges" and act as competing endogenous RNA (ceRNA). LncRNA-miRNA-mRNA or circRNA-miRNA-mRNA triple network is a significant mechanism of various biological functions of cancer.[33,34] Herein, miR-145 came into focus as it participated in diverse biological processes of cancers by regulating target genes or signaling, including tumorigenesis, proliferation, differentiation, apoptosis, metastasis, angiogenesis and therapeutic resistance. A sequence of bioinformatics prediction programs, based on mathematical algorithms, have been developed to properly identify mRNA sequences that can serve as a target for each specific miRNA. We used four algorithms to predict and analyze the hypothetical mRNA targets for miR-145, including TargetScan (http://www.targetscan.org), MiRanda (http://www.microrna.org/), MiRDB (http://www.mirdb.org/) and MiRwalks (http:// www.mirwalk.umm.uni-heidelberg.de/) (Figure 1). Finally, we screened and identified 78 overlapped potential targets by bioinformatics, which will be helpful in the future research regarding miR-145 (Tables 1 and 2).

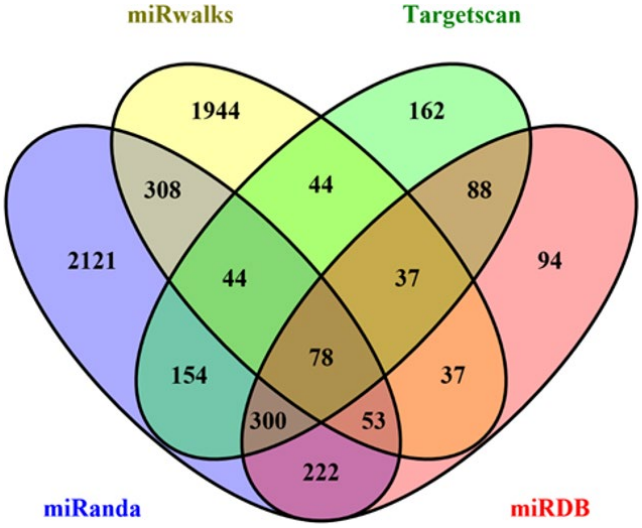

FIGURE 1 Venn diagram of potential targets of miR-145 by bioinformatics

3 | MIR-145 IN DRUG RESISTANCE

Drug resistance is a leading reason for therapeutic failure and cancer deaths. Cumulative evidence showed that miR-145 was correlated with chemotherapy resistance, suggesting that it might serve as a candidate and promising biomarker for drug resistance. There are several mechanisms contributing to chemotherapeutic drug resistance, including multidrug resistance (MDR), cancer stem cells (CSC), inhibition of cell death, alterations in the drug target, DNA repair enhancements and gene amplification.[35,36]

3.1 | Increasing drug efflux

The ATP-binding cassette (ABC) transporter family consists of 49 members, but only 3 have been studied extensively in connection with MDR. These 3 members are: (i) ABC subfamily B member 1 (ABCB1), also known as multidrug resistance protein 1 (MDR1) or P-glycoprotein (P-gp); (ii) ABC subfamily C member 1 (ABCC1), also known as MDR-associated protein 1 (MRP1); and (iii) ABC subfamily G member 2 (ABCG2), also known as breast cancer resistance protein (BCRP) or mitoxantrone-resistance gene (MXR).[37] P-gp is a versatile drug efflux pump, which includes 12 transmembrane domains and two ATP-binding sites.[38] It efficiently removes cytotoxic agents, such as doxorubicin, vinblastine and paclitaxel. Fas ligand (FasL) activation enhances chemotherapy resistance by augmenting the protein expression of P-gp through the ERK1/2 MAPK-GSK3β signaling pathway in CRC and GC. In addition, overexpression of miR-145 could downregulate P-gp as well as hamper FasL-induced upregulation of P-gp.[39] Fas belongs to the TNF

TABLE 1 Seventy-eight overlapped potential targets of miR-145 by bioinformatics

Gene symbol	Gene name
ABCE1	ATP-binding cassette, sub-family E (OABP), member 1
ABR	Active BCR-related
ACTB	Actin, beta
ADAM19	ADAM metallopeptidase domain 19
ANO6	Anoctamin 6
AP1G1	Adaptor-related protein complex 1, gamma 1 subunit
ARF6	ADP-ribosylation factor 6
ARHGAP21	Rho GTPase activating protein 21
ARHGAP28	Rho GTPase activating protein 28
ARL11	ADP-ribosylation factor-like 11
ATP1B4	ATPase, Na+/K + transporting, beta 4 polypeptide
BTG1	B-cell translocation gene 1, anti–proliferative
CAMK1D	Calcium/calmodulin-dependent protein kinase ID
CAMK2D	Calcium/calmodulin-dependent protein kinase II delta
CAPRIN1	Cell cycle associated protein 1
CAV2	Caveolin 2
CTNND1	Catenin (cadherin-associated protein), delta 1
DERL2	Derlin 2
DNAL1	Dynein, axonemal, light chain 1
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A
ERLIN1	ER lipid raft associated 1
EXOC8	Exocyst complex component 8
FAM126A	Family with sequence similarity 126, member A
FBXO34	F-box protein 34
FLT1	Fms-related tyrosine kinase 1
GCLM	Glutamate-cysteine ligase, modifier subunit
GRB10	GRB10 interacting GYF protein 1
HS6ST1	Heparan sulfate 6-O-sulfotransferase 1
JPH1	Junctophilin 1
KIF3A	Kinesin family member 3A
KLHL15	Kelch-like family member 15
KLHL18	Kelch-like family member 18
LARP4B	La ribonucleoprotein domain family, member 4B
LASP1	LIM and SH3 protein 1
LPIN2	Lipin 2
LRRC8B	Leucine rich repeat containing 8 family, member B
MPZL1	Myelin protein zero-like 1
MTX3	Metaxin 3
NAA25	N(alpha)-acetyltransferase 25, NatB auxiliary subunit
NAA50	N(alpha)-acetyltransferase 50, NatE catalytic subunit
NEDD9	Neural precursor cell expressed, developmentally down-regulated 9
NR4A2	Nuclear receptor subfamily 4, group A, member 2
NSUN4	NOP2/Sun domain family, member 4
NUDT21	Nudix (nucleoside diphosphate linked moiety X)-type motif 21
NUFIP2	Nuclear fragile X mental retardation protein interacting protein 2
PAFAH1B2	Platelet-activating factor acetylhydrolase 1b, catalytic subunit 2
PAN2	PAN2 poly(A) specific ribonuclease subunit homolog (S. cerevisiae)
PHACTR2	Phosphatase and actin regulator 2
PSAT1	Phosphoserine aminotransferase 1
PTGFR	Prostaglandin F receptor (FP)
RBM3	RNA binding motif (RNP1, RRM) protein 3
RFX3	Regulatory factor X, 3 (influences HLA class II expression)
RGPD3	RANBP2-like and GRIP domain containing 3
RREB1	Ras responsive element binding protein 1
RTKN	Rhotekin
SEL1L3	Sel-1 suppressor of lin-12-like 3 (C. elegans)
SKP1	S-phase kinase-associated protein 1
SLC25A25	Solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25

(Continues)

(Continues)

TABLE 1 (Continued)

Gene symbol	Gene name
SMCR8	Smith-Magenis syndrome chromosome region, candidate 8
SNX24	Sorting nexin 24
SNX27	Sorting nexin 27
SOCS7	Suppressor of cytokine signaling 7
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1
STAM	Signal transducing adaptor molecule (SH3 domain and ITAM motif) 1
TAGLN2	Transgelin 2
TBPL1	TBP-like 1
TET2	Tet methylcytosine dioxygenase 2
TGFBR2	Transforming growth factor, beta receptor II (70/80kDa)
TM9SF4	Transmembrane 9 superfamily protein member 4
TMOD1	Tropomodulin 1
TMOD3	Tropomodulin 3
TPM3	Tropomyosin 3
TPM4	Tropomyosin 4
TSPAN6	Tetraspanin 6
TTC14	Tetratricopeptide repeat domain 14
USP31	Ubiquitin specific peptidase 31
ZBTB33	Zinc finger and BTB domain containing 33
ZNF521	Zinc finger protein 521

and NGF transmembrane receptor superfamily, which is capable of activating caspase-dependent apoptosis.[40] In addition, miR-145 downregulated P-gp and pRb through inhibition of specificity protein 1 (Sp1) and cyclin-dependent kinase 6 (CDK6), thus promoting sensibility to paclitaxel in epithelial ovarian cancer (EOC).[11] MRP1 is similar to P-gp in structure, and structurally transport a variety of glutathione- and glucuronide-conjugated molecules.[41,42] Intriguingly, overexpression of miR-145 could enhance chemotherapeutic efficiency through inducing intracellular doxorubicin accumulation by suppressing MRP1 in breast cancer.[17] MiR-145 sensitized ESCC to cisplatin by directly inhibiting the PI3K/AKT signaling axis, which, in turn, led to a decrease of MRP1 and P-gp expression.[7] Analogously, miR-145 inhibited oxaliplatin resistance in CRC by regulating G protein coupled receptor 98 (GPR98), thus downregulating MRP1 and P-gp.[19] LINC00707 enhanced the expression of MRP1 and P-gp by sponging miR-145 in non–small cell lung cancer (NSCLC). Moreover, knockdown of LINC00707 suppressed expression of anti–apoptotic protein BCL-2 and enhanced expression of pro–apoptotic protein Bax, thus promoting cisplatin sensitivity.[4] CircPVT1 contributed to cisplatin and pemetrexed resistance in lung adenocarcinoma by positively regulating MRP1 through sponging miR-145.[3] Analogously, lncRNA CACS15 contributed to oxaliplatin resistance in CRC cancer through the miR-145/MRP1 axis.[18] The MiR-145/MRP1 axis also increased cisplatin toxicity in gallbladder cancer.[43] TGF-β1 contributed to MDR in HCC through increasing the expression of P-gp and BCRP via the SMAD4/lncRNA HOX transcript antisense RNA (HOTAIR)/miR-145 axis. TGF-β signals are transduced by the SMAD family that regulates homeostasis, proliferation, apoptosis, differentiation and tumor growth. SMAD4 functions as a shuttle between the cytoplasm and the nucleus, whose gene is located on the long arm of chromosome 18 at point 21.1[14,44,45] (Figure 2).

3.2 | Inhibition of apoptosis

Apoptosis is the program of cell death that may be triggered via numerous internal mitochondria-mediated signaling pathways (eg, BCL-2 and Bax) or external receptor-dependent stimulus (eg, FAS, TNF-R and caspases-3, -6, -7 and -8).[46] Overexpression of miR-145 obviously blocked cell viability and facilitated the cell apoptosis rate upon 5-fluorouracil (5-FU) treatment through downregulation of reversionless 3-like (REV3L) in ESCC. Meanwhile, miR-145 was more efficient in modulating apoptotic proteins, whose overexpression induced a prominent decrease of BCL-2 expression and an increase of Bax and cleaved caspase-3 expression, thus activating pro–apoptotic activity.[8,47] As the catalytic subunit of DNA polymerase ζ, REV3L is overexpressed and mutated in several cancers and has been validated as a contributor of chemotherapy resistance.[48-50] MiR-145-3p enhanced bortezomib sensitivity by targeting histone deacetylase 4 (HDAC4) in multiple myeloma. Furthermore, suppression of HDAC4 upregulated pro–apoptotic protein BCL2L11 and caused MTORC1 inactivation, thereby promoting autophagy and cell death. Histone deacetylases control a broad array of tumor biological processes, such as apoptosis, survival and autophagy.[51,52] MiR-145 enhanced cell sensitivity to cetuximab by stimulating cetuximab-mediated antibody-dependent cellular cytotoxicity (ADCC) in colon cancer. Elevated apoptosis was observed during ADCC, which could be explained partly by the reduced BCL-2, increased caspase-3/7 and granzyme B activity. Granzyme B can target both cytosolic and nuclear substrates to induce apoptosis, and its most distinguished function is the direct cleavage of caspase-3.[53,54] Nuclear factor-κB (NF-κB) is a prosurvival transcription factor, whose transcriptional targets are anti–apoptotic proteins. APRIL attenuated therapeutic efficacy via activation of the NF-κB pathway in GC, whose expression was regulated by miR-145. APRIL, a member of the TNF family, was reported to function in sustaining lymphocytic leukemia B cell survival. MiR-145 represented a therapeutic target to overcome chemotherapeutic resistance, which reversed APRIL-mediated cisplatin resistance via directly targeting its 3′-untranslated region (3′-UTR).[26,55]

TABLE 2 Summary of target genes and therapeutic agents of miR-145 in cancer therapy resistance

Tumor	Target(s)	Therapeutic agents	References
NSCLC	ADAM19	Gefitinib	Wang et al[5]
	EGFR	Erlotinib	Amri et al[6]
	MRP1 and P-gp	Cisplatin	Zhang et al[4]
	CDK6	Cisplatin	Bar et al[76]
	KLF4	Cisplatin	Cui et al[65]
Lung adenocarcinoma	FSCN1	Docetaxel	Pan et al[69]
	MRP1	Cisplatin and pemetrexed	Zheng et al[3]
CRC	GPR98	Oxaliplatin	Fu et al[19]
	MRP1	Oxaliplatin	Gao et al[18]
	RAD18	5-FU	Liu et al[20]
	KLF4 and c-Myc	Radiation	Zhu et al[9]
Colon cancer	OCT4, SOX2, Nanog	Cisplatin and paclitaxel	Yan et al[66]
CRC and GC	P-gp	5-FU, SN38, or Oxaliplatin	Zheng et al[39]
GC	APRIL	Cisplatin	Zhi et al[26,55]
	CD44	5-FU and cisplatin	Zeng et al[25]
HCC	P-gp and BCRP	Imatinib	Kong et al[14]
	RAD18	Radiation	Chen et al[16]
	SMAD3	Doxorubicin	Ju et al[37]
Esophageal carcinoma	MRP1 and P-gp	Cisplatin	Zheng et al[39]
	REV3L	5-FU	Chen et al[8]
	P70S6K1	Radiation	Wang et al[88]
Ovarian cancer	Sp1 and CDK6	Paclitaxel	Zhu et al[11]
	c-Myc	Cisplatin	Sheng et al[10]
Cervical cancer	HLTF	Radiation	Ye et al[28]
Breast cancer	MRP1	Doxorubicin	Gao et al[17]
Prostate cancer	AKAP12	Docetaxel	Xue et al[22]
	RAD51, Mcl1, Par-4 and PARP1	Radiation	Gong et al[23]
Bladder cancer	HMGA2 and KLF4	Gemcitabine	Zhuang et al[24]
Pancreatic Adenocarcinoma	P70S6K1	Gemcitabine	Lin et al[27]
Gallbladder cancer	MRP1	Cisplatin	Zhan et al[43,59]
Nasopharyngeal carcinoma	SOX2	Cisplatin	Chan et al[63]
Multiple myeloma	HDAC4	Bortezomib	Wu et al[51]

Note: CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; NSCLC, non–small-cell lung cancer

3.3 | Cancer stem cells

Emerging data showed that CSC represented a small subpopulation of cells within most solid and hematologic cancers, and were vital mediators and drivers in chemotherapy and radiation resistance.[56-58] MiR-145 provided a therapeutic scheme to inhibit the CSC-like properties of GC, and lowered 5-FU and cisplatin chemoresistance by targeting CD44, an integral cell membrane glycoprotein.[25] CD44 is a helpful CSC marker for verifying and isolating CSC from a panel of gastric cancer cell lines, and may be a driving factor in the evolution of CSC.[59-61] Wnt signaling is a crucial CSC self-renewal signaling pathway.[62] MiR-145 enhanced chemosensitivity to demethoxycurcumin by targeting the SOX2-Wnt/β-catenin axis in glioma. SOX2, a pluripotent stem cell marker, plays a pivotal role in maintaining the undifferentiated situation and proliferation of stem cells.[12] CREB-binding protein (CBP) is a Wnt signaling component, and is frequently activated in nasopharyngeal carcinoma. A specific CBP/β-catenin antagonist was identified to repress the CSC-like population through restoration of miR-145, which directly targeted SOX2. Moreover, it effectively suppressed the growth of nasopharyngeal carcinoma when combined with cisplatin.[63] The elevated TGF-β1 induced a regulatory axis of lncRNA-LET/NF90/miR-145 to increase CSC populations and promote gemcitabine resistance through upregulation of stemness markers HMGA2 and KLF4 in bladder cancer.[24] Kruppel-like factor 4 (KLF4) is a transcription factor expressed

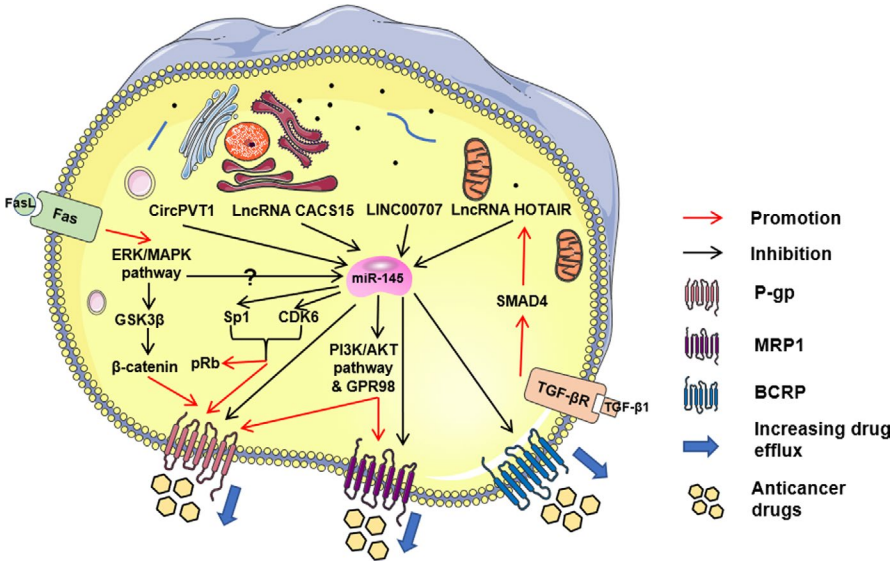

FIGURE 2 Regulatory mechanisms of miR-145 in cancer therapy resistance by increasing drug efflux. MiR-145 was sponged by circPVT1, lncRNA CACS15, LINC00707 and lncRNA HOTAIR, which blocked the downstream PI3K/AKT signaling or target genes, thus directly or indirectly inhibiting P-gp, MRP1 and BCRP

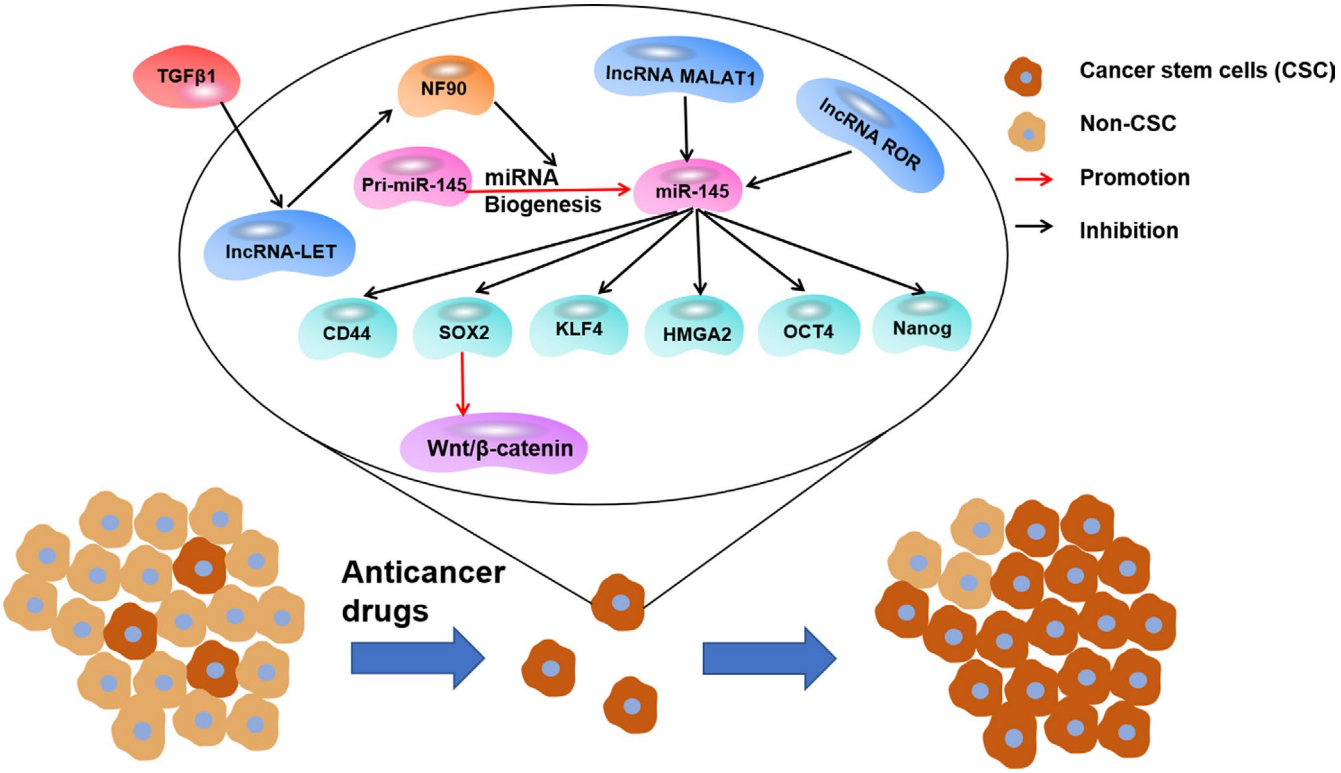

FIGURE 3 Regulatory mechanisms of miR-145 in cancer therapy resistance by inhibiting cancer stem cells (CSC) properties. MiR-145 was sponged by lncRNA-LET, lncRNA MALAT1 and lncRNA ROR, and concomitantly suppressed CD44, SOX2, KLF4, HMGA2, OCT4 and Nanog

in various human tissues, which controls cell reprogramming and sustains stemness maintenance.[64] LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) contributed to cisplatin resistance by regulating the miR-145/KLF4 axis in NSCLC.[65] Likewise, lncRNA ROR sponged miR-145 to prevent OCT4, SOX2 and Nanog in colon CSC, thereby increasing the stem cell phenotype, and then enhanced chemoresistance to cisplatin and paclitaxel[66] (Figure 3).

3.4 | Other mechanisms

Other mechanisms engaged in chemotherapy resistance and impairing therapy efficacy mainly involve epithelial–mesenchymal transition (EMT), metabolic changes, DNA damage repair and immune tolerance. EMT is a universal phenomenon in cancers, in which epithelial cells are transformed into a mesenchymal phenotype.[67] Furthermore, EMT is verified to participate in the drug

resistance of cancer cells.[68] The LncRNA ROR/miR-145/FSCN1 axis effectively reversed EMT in docetaxel-resistant lung adenocarcinoma cells and sensitized them to chemotherapy.[69] MiR-145 increased the doxorubicin cytotoxicity in chemoresistant tumor cells via EMT through downregulating SMAD3 in HCC.[15] SMAD3, another member of the SMAD family, serves as a substrate for TGF-β and commonly called receptor-regulated SMAD.[44,70] Tumor suppressor miR-145 reversed 5-FU resistance by directly targeting DNA damage-related gene RAD18 in CRC. RAD18, a DNA damage-activated E3 ubiquitin ligase, is known to play a critical role in DNA damage repair in cancer cells.[20] MiR-145 increased the sensitivity of pancreatic adenocarcinoma cells to gemcitabine treatment, providing new insight into the role of miR-145/P70S6K1/HIF-1α/VEGF in mediating gemcitabine chemosensitivity.[27] Hypoxia-inducible factor 1 (HIF1), a critical player in the Warburg effect, binds to hypoxia response elements on DNA and stimulates VEGF gene transcription. In addition, emerging evidence has shown that the Warburg effect promotes drug resistance.[71,72] Accumulating studies have reported the activation of EGFR as a resistance mechanism to chemotherapy.[73,74] Targeting EGFR by miR-145 inhibited cell growth and sensitized NSCLC cells to erlotinib.[6] LncRNA MALAT1 enhanced the docetaxel resistance of prostate cancer cells via miR-145-5p-mediated regulation of AKAP12.[22] MiR-145 enhanced the sensitivity of NSCLC to gefitinib through targeting ADAM19.[5] A disintegrin and metalloproteinases (ADAMs) are zinc-dependent, membrane-associated metalloproteinases. ADAM19 is known to be involved in extracellular matrix breakdown and catalytically mediated ectodomain shedding of substrates such as TNF-α.[75] CDK6 was identified as a potential miR-145 target and cisplatin sensitivity mediator in NSCLC. Notably, this suggested that the inhibitor of CDK4/6 should be avoided during cisplatin therapy.[76] Immune tolerance is one of the leading causes of chemotherapy resistance in carcinoma cases. Programmed death-ligand 1 (PD-L1) is an inhibitory molecule expressed by cancer cells, which plays a significant role in immune tolerance through the induction of T cell dysfunction. The MiR-145/c-Myc/PD-L1 axis contributed to cisplatin resistance in ovarian cancer.[10]

4 | MIR-145 IN RADIOTHERAPY RESISTANCE

Ionizing radiation (IR) induces a complicated cellular reaction involving affluent molecular pathways. MiR-145 was also shown to function in mediating resistance to the cytotoxic action of IR. DNA repair enzymes and anti–apoptotic proteins were highly expressed in radio-resistant cancer cells.[77] MiR-145 appeared to dramatically sensitized cancer cells to radiation by reducing the efficiency of the repair of radiation-induced DNA double-strand breaks. Certainly, we need to further study this to determine more specific mechanisms of the radiosensitizing effect of miR-145. Elevated expression of miR-145 contributed to promoting radiosensitivity of prostate cancer, potentially by downregulating DNA repair via targeting Par-4, PARP, RAD51 and Mcl1.[23] Mitotic catastrophe was dramatically increased in cells receiving miR-145 and radiation. Par-4, a pro–apoptotic gene, repressed radiation-induced NF-κB activity and BCL-2 expression, resulting in an increase of radiosensitivity in prostate cancer.[78] PARP1 played a profound role in the repair of radiation-induced DNA damage, indicating its inhibition might serve as a promising mechanism for promoting radiosensitivity.[79,80] Downregulation of RAD51 gene expression was reported to enhance sensitivity to gamma radiation in glioma,[81] while the Mcl-1 enhanced radiosensitivity of pancreatic carcinoma in vitro.[82] CSC phenotype and EMT cooperated to impact therapeutic resistance in epithelial tumors such as CRC. The zinc finger molecule snail family transcriptional repressor 1 (SNAI1) is a transcriptional factor that plays a critical role in provoking EMT. MiR-145 delivery could reverse SNAI1-mediated radiation resistance in CRC. Increased expression of SNAI1 maintained the stemness and induced expression of the CSC-related transcription factor Nanog, and further conferred CRC cells a radiation-resistant phenotype.[9] MiR-145 is a profound component of the p53 regulatory network.[83] The tumor suppressor p53 transcriptionally induced the expression of miR-145 by interacting with a potential p53 response element in the miR-145 promoter[67]. LncRNA ROR enhanced radiotherapy resistance for CRC by negatively regulating the p53/miR-145 pathway, which functioned as a p53 repressor in response to DNA damage.[21] In addition, lncRNA ROR was reported to enhance the efficacy of radiotherapy in HCC, which exerted its biological function by sponging miR-145 to modulate RAD18 expression, thereby promoting DNA repair.[16] LncRNA CCAT2 enhanced radioresistance via targeting the miR-145/p70S6K1 and p53 pathway in esophageal carcinoma, hinting that it would be a potential strategy for enhancing the efficacy of radiotherapy.[84] Restoration of miR-145 expression reduced radioresistance by targeting HLTF in cervical cancer, a DNA damage repair-associated gene. Radiation-induced DNA damage activated p53, and activated p53 ultimately contributed to the radiosensitizing effect by regulating miR-145/HLTF axis.[28]

5 | CONCLUSIONS AND PROSPECTS

Chemotherapy and radiotherapy are critical treatment strategies for cancer patients. These strategies are occasionally insufficient to improve poor prognosis due to therapeutic resistance. Cancers are sophisticated, dynamic systems that start to evolve resistance strategies immediately with the application of therapies. Remaining tumor cells become therapy-resistant in some patients over the duration of treatment, resulting in relapse and metastasis.[35,36,85] Resistance to chemotherapy and radiotherapy is a major obstacle facing current cancer research. Numerous mechanisms may be involved in the therapeutic resistance of cancer, among which miR-145 plays a pivotal role in the acquisition of therapeutic resistance indicated by accumulating evidence. The aforementioned discussion

disclosed the latent role of miR-145 as both a predictive marker of response and a new therapeutic target, which could further enhance the efficacy of chemotherapy and radiotherapy. Collectively, developing successful therapeutic strategies will require scientists to identify and comprehend the resistance-inhibiting effects of miR-145. Given their intrinsic properties, miR-145 could serve as a novel biomarker and promising therapeutic target for cancer, and may provide new insights into the diagnosis of patients at early stages, prediction of prognosis, and screening of the patients in response to therapy, although further investigation is required before application in the clinic.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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