miR-944 in Cancer

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miR-944 is localized in intron 4 of TP63. ΔNp63 in intron 3 of TP63 recruits the transcription factor AP-2 to promote miR-944 gene expression, which mediates epidermal differentiation induction by ΔNp63. miR-944 is dysregulated in various cancers. In squamous cell carcinoma. miR-944 can target and inhibit 27 protein-coding genes, thereby regulating cell cycle, proliferation, apoptosis, epithelial mesenchymal transition, cancer cell invasion and migration, and other cell behaviors. The genes targeted by miR-944 are involved in three signaling pathways, including the Wnt/β-catenin pathway, Jak/STAT3 pathway, and PI3K/AKT pathway. miR-944 was regulated by a total of 11 competing endogenous RNAs, including 6 circular RNAs and 5 long non-coding RNAs. Abnormally expressed miR-944 can act as an independent prognostic factor and is closely related to tumor invasion, lymph node metastasis, TNM staging, and drug resistance. miR-944 is expected to become a critical biomarker with great clinical application value in cancer.

miR-944 ceRNA dysregulation diagnosis

1. Introduction

microRNAs (miRNAs) are endogenous short non-coding RNAs of approximately 22 nt that typically target the 3’ untranslated region (3’-UTR) of mRNAs [1], thereby inhibiting the function of protein-coding genes [2]. Dysregulation of miRNAs is often associated with the malignant transformation of cells, thereby participating in biological processes that promote cancer progression, metastasis, and treatment resistance [3][4].

miR-944 is located in the fourth intron of tumor protein p63 (TP63) in the chromosome 3q28 region [5] and produced at the 3’ end of the stem-loop structure of pre-mir-944. miR-944 is aberrantly expressed in more than 10 cancers. Targeted inhibition of mRNA by miRNA can be hindered by competing endogenous RNAs (ceRNAs), such as circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) [6]. miR-944 is regulated by eleven ceRNAs, including six circRNAs and five lncRNAs. miR-944 can target and suppress 27 protein-coding genes, thereby regulating cancer cell behaviors such as cancer cell cycle, growth, proliferation, epithelial-mesenchymal transition (EMT), cancer cell invasion, and metastasis. The genes targeted by miR-944 are involved in three signaling pathways, including the Wnt/β-catenin pathway, the Jak/STAT3 pathway, and the PI3K/AKT pathway.

In patients with nasopharyngeal carcinoma (NPC) [7], colorectal cancer (CRC) [8][9], or breast cancer (BrC) [10], low expression of miR-944 was not only associated with poorer overall survival (OS) but also with more advanced tumor infiltration, more lymph node metastasis, and more advanced tumor node metastasis (TNM) stage [9]. miR-

944 is associated with resistance to four anticancer drugs, including cisplatin (DDP) [11], rapamycin (RAPA) [12], doxorubicin (DOX) [13], and paclitaxel (PTX) [14]. miR-944 is involved in the molecular mechanism of action of two anticancer drugs, including the quinazolidine alkaloid matrine [15] and a drug under clinical trials, 188Re-liposome [16].

2. miR-944 and Its Host Gene TP63

The p63 transcription factor encoded by TP63, the host gene of miR-944, is a tumor suppressor gene belonging to the p53 family [17]. N-terminal truncated isoform of p63 (ΔNp63), which is transcribed from an alternative promoter in intron 3 of TP63, can regulate the epithelial properties of cells and play an important role in the terminal differentiation and stemness maintenance of basal epidermal cells [18]. miR-944 was significantly positively correlated with ΔNp63 expression in cervical cancer (CxCa) and jointly exerted a cancer-promoting effect [19]. During the differentiation of human epidermal keratinocytes, ΔNp63 can recruit the transcription factor AP-2 to the promoter region of the miR-944 gene, thereby promoting the expression of miR-944 and inducing epidermal differentiation [17].

3. Aberrant Expression of miR-944 in Cancer

As shown in **Table 1**, miR-944 is downregulated in cells and tissues of 11 cancers. Meanwhile, miR-944 is lowly expressed in the plasma of esophageal cancer (ECa) [20]. It is worth noting that miR-944 is highly expressed in cancer tissues of LUSC [21] and endometrial carcinoma (EC) [22], as well as CxCa cell lines, serum, and tissues [5][23][24][25]. Furthermore, the expression of miR-944 in BrC is controversial. Specifically, miR-944 was highly expressed in serum and tissues of BrC [26], whereas miR-944 was found to be downregulated in five BrC cell lines and tissues [27].

Table 1. Aberrant expression of miR-944 in different cancers.

Physiological System	Cancer	miR-944 Expression	Cell Line	Tissue or Serum	Ref.
Nervous system	GBM/LGG	Downregulated	HA1800 versus SHG44, U87MG, and U251MG	Paracancerous tissues versus glioma tissues from 5 patients	[28]
Respiratory system	NPC	Downregulated	NP69 versus C666-1, CNE1, CNE2, and HNE1	Paracancerous tissues versus tumor tissues from 20 NPC patients	[29]
		Downregulated	NP69 versus CNU46, SUNE1, HONE1, 6–10 B, CNE1, CNE2, and HNE1	Nasopharyngeal mucosa tissues from 30 healthy people versus primary tumor tissues from 30 NPC patients	[7]

Physiological System	Cancer	miR-944 Expression	Cell Line	Tissue or Serum	Ref.
Digestive system	LUAD	Downregulated	16HBE versus A549, H1299, SK-Lu-1, and PC-9	Paracancerous tissues versus LUAD tissues from 25 patients	[30]
	LUSC	Upregulated	—	Paracancerous tissues from patients versus SCC tissues from patients	[21]
	NSCLC	Downregulated	BEAS-2B versus H522 and H1975	—	[15]
		Downregulated	BEAS-2B versus H358, H1299, PC-9, and A549	Paracancerous tissues versus tumor tissues from 65 NSCLC patients	[31]
		Downregulated	BEAS-2B versus A549, H226, H292, ANP973, and H1299	Paracancerous tissues versus tumor tissues from 60 NSCLC patients	[32]
		Downregulated	—	Paracancerous tissues versus tumor tissues from 9 NSCLC patients	[2]
	TSCC	Downregulated	normal gingival epithelial cells versus SCC-9, CAL-27, and SCC-15	Paracancerous tissues versus TSCC tissues from 57 patients	[33]
	ECa	Downregulated	—	Paracancerous tissues versus adenocarcinoma tissues from 59 eca patients; serum exosomes from healthy persons versus serum exosomes from 59 eca patients	[20]
	GC	Downregulated	GES-1 versus AGS, MKN-1, HGC-27, MKN-45, SGC-7901, and BGC-823	—	[34]
		Downregulated	GES-1 versus SGC-7901, MGC-803, MKN-28, and BGC-823	Paracancerous tissues versus tumor tissues from 40 GC patients	[35]

Physiological System	Cancer	miR-944 Expression	Cell Line	Tissue or Serum	Ref.
Reproductive system	HCC	Downregulated	L02 versus Hep3B, Bel-7402, SMMC-7721, Huh7, and SK-HEP-1	Paracancerous tissues versus tumor tissues from 61 HCC patients	[36]
	CRC	Downregulated	HIEC and HEK293 versus HCT116, Caco-2, HT29, SW620, and SW480	—	[9]
		Downregulated	COS7 versus HCT116, LoVo, RKO, HCT15, HT29, SW480, and SW620	—	[37]
		Downregulated	—	Paracancerous tissues versus fresh CRC tissues from 140 CRC patients	[8]
		Downregulated	CCC-HIE-2 versus HT-29, HCT116, SW480, and SW620	Paracancerous tissues versus fresh CRC tissues from 100 CRC patients	[38]
	EC	Upregulated	—	Normal endometrial tissues from 20 non-cancer patients versus tumor tissues from 68 EC patients	[22]
	CxCa	Upregulated	—	Paracancerous tissues versus tumor tissues from 27 cxca patients	[25]
		Upregulated	—	Serum specimens from 24 women with localized disease versus serum specimens from 25 women with metastatic disease	[24]
		Upregulated	HcerEpiC versus HeLa, CaSki, SiHa, and C33A	Paracancerous tissues versus fresh cxca tissues from 70 cxca patients	[23]
		Upregulated	—	50 FFPE normal cervical tissue samples versus 66 FFPE cxca tissue samples	[5]

Physiological System	Cancer	miR-944 Expression	Cell Line	Tissue or Serum	Ref.
Motor system	BrC	Downregulated	MCF-10A versus MDA-MB-231, MCF-7, MDA-MB-453, ZR-75, and T47-D	Paracancerous tissues versus locally invasive breast tumors tissues from brc patients	[27]
		Upregulated	—	Paracancerous tissues versus tumor tissues from 40 brc patients; serum samples from 30 healthy people versus serum samples from 30 brc patients	[26]
	SaOS	Downregulated	hFOB1.19 versus MG-63, SAOS-2, HOS, and U2OS	Paracancerous tissues versus tumor tissues from 38 saos patients	[39]
	COF	Downregulated	—	Bone tissues from 10 healthy people versus bone tissues from 9 COF patients	[3]

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Figure 1. Pan-cancer analysis of miR-944 based on TCGA database. (**A**) Histogram of median quantile expression of miR-944 in non-tumor and tumor groups in the TCGA database. The blue font indicates that miR-944 is significantly low expressed in this cancer type; the red font indicates that miR-944 is significantly highly expressed in this cancer type; (**B**) comparison of miR-944 expression levels between non-tumor and tumor groups in the TCGA database. *** means $p < 0.0000625$; ** means $p < 0.000625$; * means $p < 0.003125$; ns means no significant difference; (**C**) overview of SNVs of TP63; (**D**) mutation types in TP63 protein domains in various cancers; (**E**) differences in the expression level of miR-944 between the TP63 mutant group (Mut) and the wild group (WT). Ns means no significant difference. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; STAD, stomach adenocarcinoma; SKCM, skin cutaneous melanoma; TGCT, testicular germ cell tumor; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

Researchers compared differences in miR-944 expression between non-tumor and tumor samples of 16 cancer types (unpaired Wilcoxon test, R version 4.1.3). As shown in **Table 2** and **Figure 1**B, researchers found that miR-944 was significantly upregulated in five tumors (BLCA, HNSC, LUSC, THCA, and UCEC); significantly downregulated in two tumors (BRCA and PRAD) (**Figure 1**B). Notably, the TCGA analysis demonstrated the association of miR-944 expression with cancer risk in bladder cancer, head and neck squamous cell carcinoma (HNSCC), thyroid cancer, and prostate cancer, which has not been reported yet.

Table 2. Comparison of miR-944 in TCGA dataset with existing data.

TCGA Cancers	Sample Size (T/N)	miR-944 Expression in TCGA	miR-944 Expression in the Present Studies
BLCA	405/18	Upregulated; Q4	Not studied
BRCA	624/74	Downregulated; Q4	Downregulated in BrC tissues and BrC cells (MDA-MB-231, MCF-7, MDA-MB-453, ZR-75, and T47-D) [27]; and Upregulated in BrC tissues and serum sample of BrC patients [26]
CHOL	20/8	ns; Q3	Not studied
ESCA	176/8	ns; Q4	Downregulated in ECa tissues and serums of ECa patients [20]

TCGA Cancers	Sample Size (T/N)	miR-944 Expression in TCGA	miR-944 Expression in the Present Studies
GBM/LGG	209/3	ns; Q3	Downregulated in GBM/LGG tissues and GBM/LGG cells (SHG44, U87MG, and U251MG) [28]
HNSC	485/44	Upregulated; Q4	Not studied
KICH	49/8	ns; Q3	Not studied
KIRC	108/19	ns; Q3	Not studied
KIRP	155/23	ns; Q3	Not studied
LIHC	324/47	ns; Q4	Downregulated in HCC tissues and HCC cells (Hep3B, Bel-7402, SMMC-7721, Huh7, and SK-HEP-1) [36]
LUAD	430/40	ns; Q4	Downregulated in LUAD tissues and LUAD cells (A549, H1299, SK-Lu-1, and PC-9) [30]
LUSC	334/44	Upregulated; Q4	Upregulated in LUSC tissues [21]
PRAD	437/50	Downregulated; Q4	Not studied
STAD	303/26	ns; Q3	Downregulated in GC tissues and GC cells (AGS, MKN-1, HGC-27, MKN-45, SGC-7901, MGC-803, BGC-823, and MKN-28) [34][35]
THCA	420/50	Upregulated; Q4	Not studied
UCEC	330/26	Upregulated; Q3	Upregulated in EC tissues [22]

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was no significant difference in the expression level of miR-944 between males and females in cancer. In BLCA and ESCA, the level of miR-944 in whites was significantly lower than that in other races.

Q3, 0.5–0.75 quantile; Q4, 0.75–1.0 quantile; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PRAD, prostate adenocarcinoma; STAD, stomach adenocarcinoma; THCA, thyroid carcinoma; UCEC, uterine corpus endometrial carcinoma.

4. Co-Expression of TP63 Transcripts and miR-944

miR-944 is located in the TP63. Previous studies have shown that ΔNp63, but not TAp63, can directly regulate the expression level of miR-944 by recruiting the transcription factor AP-2 [19]. The high correlation between the expression of TAp63 and miR-944 may be due to the common upstream regulators of TAp63 and ΔNp63, resulting in a significant positive correlation between TAp63 and ΔNp63.

In order to explore the relationship between TP63 and miR-944, researchers obtained the expression data of miR-944, TAp63, and ΔNp63 in TCGA (pan-cancer) from the UCSC Xena database (https://xenabrowser.net (accessed on 20 June 2022)).

Among 30 cancer types, researchers calculated pairwise correlations between miR-944, TP63, and ΔNp63 (Pearson's correlation test). As shown in **Figure 2**, miR-944 expression was significantly positively correlated with TAp63 and ΔNp63 in 15 and 16 cancers, respectively ($p < 0.01$ and $r > 0.5$). In ACC, CHOL, OV, PCPG, and

READ, the expression level of miR-944 was not significantly correlated with TAp63 and ΔNp63 ($p > 0.05$ or $r < 0.3$). Among them, the number of ACC ($n = 19$) and CHOL ($n = 20$) samples is small, which may lead to the above insignificant correlation. In KIRC and KICH, the expression of miR-944 was not significantly correlated with ΔNp63 ($p > 0.05$ or $r < 0.3$) but had a positive correlation with TAp63 ($p < 0.01$ and $r > 0.45$), suggesting that there may be a different regulatory mechanism of miR-944 expression in KIRC and KICH.

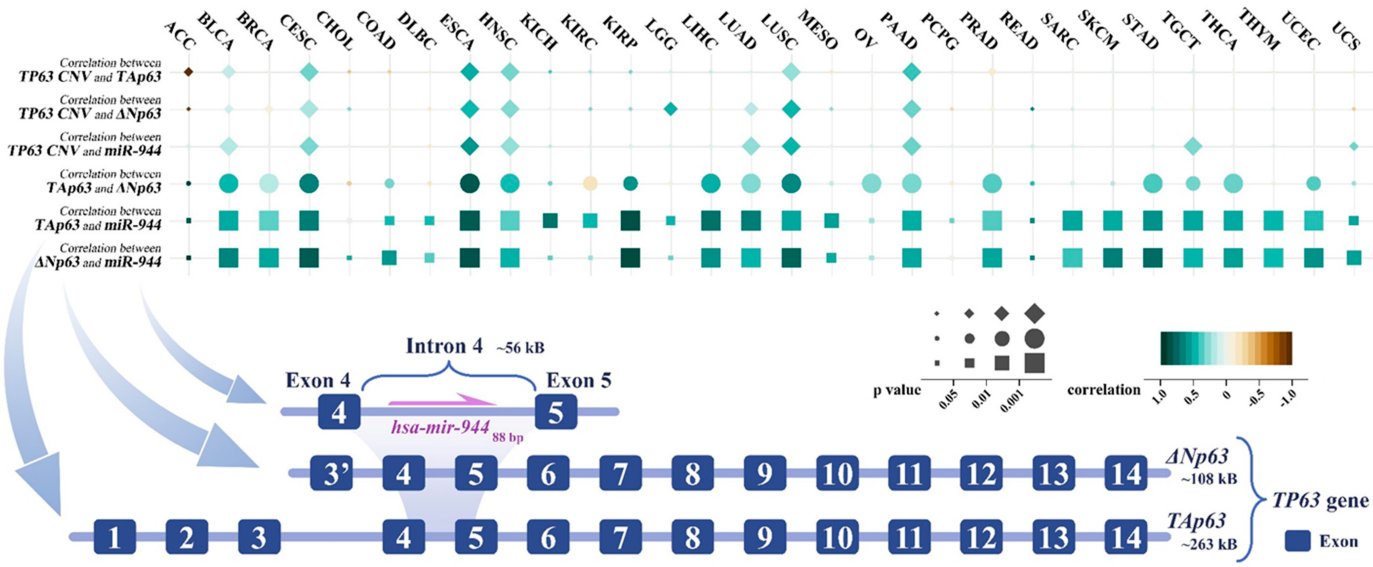

Figure 2. The correlation of miR-944 with TP63 CNV, TAp63, and ΔNp63. The figure indicates the position of hsa-mir-944 in the TP63 gene and shows the correlation of miR-944 with TP63 CNV and the expression of TAp63 and ΔNp63. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; STAD, stomach adenocarcinoma; SKCM, skin cutaneous melanoma; TGCT, testicular germ cell tumor; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma.

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