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REVIEW

Understanding the CREB1-miRNA feedback loop in human malignancies

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Abstract cAMP response element binding protein 1 (CREB1, CREB) is a key transcription factor that mediates transcriptional responses to a variety of growth factors and stress signals. CREB1 has been shown to play a critical role in development and progression of tumors. MicroRNAs (miRNAs) are a class of non-coding RNAs. They post-transcriptionally regulate gene expression through pairing with the 3′-UTR of their target mRNAs and thus regulate initiation and progression of various types of human cancers. Recent studies have demonstrated that a number of miRNAs can be transcriptionally regulated by CREB1. Interestingly, CREB1 expression can also be modulated by miRNAs, thus forming a feedback loop. This review outlines the functional roles of CREB1, miRNA, and their interactions in human malignancies. This will help to define a relationship between CREB1 and miRNA in human cancer and develop novel therapeutic strategies.

Keywords CREB1 · miRNA · Transcription factor · Feedback loop · Cancer

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Introduction

Cancer is a complex disease that arises through a multi-step process. Acquisition of cancer cell features involves changes in the wiring of signaling pathways that are tightly regulated to control processes such as cell proliferation, apoptosis, and metastasis [1]. Many of the signal transductions assemble to modulate gene expression at transcriptional level via activation or repression of transcription factors. Under different pathological conditions, the transcription factors aberrantly initiate the transcription of cancer-related genes, thereby increasing cell proliferation, differentiation, angiogenesis, and suppressing apoptosis or cell-cell adhesion, which in turn lead to cancer development [2, 3].

cAMP response element binding protein 1 (CREB1, CREB) is a key transcription factor belonging to the basic leucine zipper (bZIP) family [4]. CREB1 is activated through phosphorylation at Ser133 and/or by nuclear translocation of CREB1 coactivators [5]. It has been found to mediate transcriptional responses to a variety of growth factors and stress signals [6] (Fig. 1). Recently, the roles of CREB1 in tumorgenesis have also been established in many types of solid tumors and hematological malignancies [6, 7]. Genome-wide studies have shown that the number of putative CREB1 target genes was approximately 4000 or nearly one-quarter of the human genome [8, 9]. Researches on the targets of CREB1 used to be limited to protein-coding genes [10, 11]; however, the non-coding targets deserve further investigation.

MicroRNAs (miRNAs) are a class of non-coding RNAs that post-transcriptionally regulate gene expression through imperfect pairing with the 3′-UTR of their target mRNAs, by inducing translational repression or degradation of mRNAs [12]. MiRNAs have critical functions across various biological processes, including cell development, differentiation, apoptosis, and proliferation. First identified in B cell

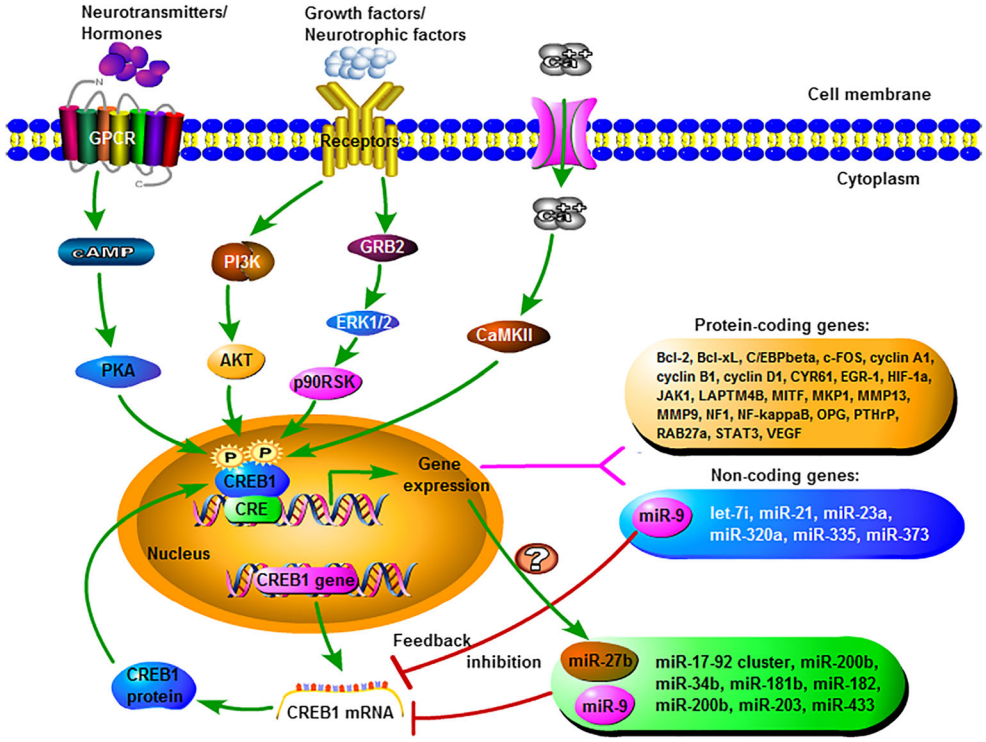

Fig. 1 A schematic model of CREB1 regulation in human cancers. CREB1 binds to the conserved cAMP-responsive element (CRE) on the promoter and mediates transcriptional responses to a variety of stimuli including neurotransmitters, hormones, membrane depolarization, and growth and neurotrophic factors, thereby acting as a mediator between different signal pathways and the downstream target genes transcription. The targets of CREB1 including both protein-coding (e.g., Bcl-2, cyclin D1, MMPs) and non-coding genes (e.g., miR-9, miR-23a, miR-373). Interestingly, CREB1 could also be negatively regulated by miRNAs (e.g., miR-9, miR-34b, miR-200b), forming a negative feedback loop. MiR-27b directly inhibits CREB1 expression and contains putative CREB1 binding sties. Whether miR-27b is transcriptionally induced by CREB1 deserves further experimental validation. Illustration of the upstream regulators of CREB1 was partially modified from pathway information provided by BioCarta (http://cgap.nci.nih.gov/Pathways/BioCarta_Pathways)

chronic lymphocytic leukemia (CLL) [13], miRNA alterations have been involved in the initiation and progression of many types of human cancers [14–21]. MiRNA has also been associated with diagnosis, prognosis, and response to treatment in human malignancies [15, 18]. MiRNAs may function as oncogenes or tumor suppressors in the majority of human cancers [19]. For example, miR-15a and miR-16-1 generally function as tumor suppressors and downregulate BCL2 in chronic lymphocytic leukemias and cyclin D1 in prostate cancer and mantle cell lymphoma [22]. Of particular interest is miR-21 which tends to function as an oncogene. This miRNA has been shown to be consistently upregulated in various cancers including lung cancer, stomach cancer, prostate cancer, colon cancer, ovarian carcinoma, B cell lymphoma, hepatocellular carcinoma (HCC), cervical cancer, chronic lymphocytic leukemia, and breast cancer [23]. All in all, alterations of miRNA expression have been reported in a variety of cancers and are implicated in various processes during tumor initiation and progression.

Although many reasons, such as genetic abnormalities, epigenetic regulation, post-transcriptional modulation, as well as transcription factor control have been described, the causes of miRNA aberrant expression in tumors are not well understood [19]. The promoter regions of miRNA genes are highly similar to those of protein-coding genes, which contain CpG islands, TATA box sequences, initiation elements, and certain histone modifications [24, 25]. A myriad of transcription factors are involved in miRNA genes transcription in cells [26, 27]. The transcription factors regulate miRNA expression positively or negatively in a tissue-specific or development-specific manner. For example, MYC stimulates expression of the miR-17-92 oncogenic cluster in lymphoma cells [27] but inhibits expression of several tumor suppressor miRNAs (for example, miR-15a), which promote MYC-mediated tumorgenesis [28]. Recently, CREB1 has been reported to modulate the expression of several miRNAs in human cancers, including miR-9 in glioma [29] and miR-373 in pancreatic cancer [30]. Interestingly, miRNAs frequently act with CREB1 in regulatory networks via feedback loops. For instance, miR-9, which is under CREB1's control, directly targets CREB1 to inhibit the proliferation of glioma cells [29]. In light of the rapid pace of research into CREB1 and miRNAs in human cancers, we perform this review for a better understanding of the CREB1-miRNA feedback loop.

Expression and function of CREB1 in human cancers

Accumulating evidence has shown that CREB1 is over-expressed in numerous human cancers, including astrocytoma, breast cancer, gastric cancer, glioma, HCC, mesothelioma, non-small cell lung cancer (NSCLC), ovarian cancer, and prostate cancer (Table 1). CREB1 is a transcription factor which functions as an oncogene that involves in the proliferation, survival, and metastasis of tumor cells [47]. For instance, CREB1 is elevated in breast cancer tissues and metastatic cancer cells and associated with poor prognosis, metastatic potential, and nodal involvement [32, 33]. CREB1 is further shown to positively regulate the proliferation, metastasis, and bone destruction of breast cancer [32]. Seo et al. shows that CREB1 is highly expressed in most of the NSCLC cell lines and associates with decreased survival in patients with NSCLC [43]. CREB1 inactivation suppresses the growth of NSCLC cells and induces apoptotic cell death [42]. Tan and colleagues find that CREB1 is over-expressed in gliomas, and promotes gliomagenesis by inducing the expression of oncogenic miR-23a, which represses the tumor suppressor PTEN [37]. More recently, Barresi et al. find the correlation between high expression of phosphorylated CREB1 (p-CREB1) and angiogenesis, recurrence risk, and poor disease-free survival in patients with meningiomas [40]. They also demonstrate that astrocytomas and oligodendrogliomas are characterized by distinctive patterns of p-CREB1 expression, which provide the evidence that CREB1 may function as a useful tool in the differential diagnosis of these two main types of gliomas [48]. Previous studies from our laboratory and others indicate that CREB1 is positively correlated with tumor metastasis, tumor stage, poor prognosis, and cancer cell growth in gastric cancer [36, 49]. In addition to its dysregulation in solid tumors, CREB1 overexpression is also associated with poor outcome of acute myelocytic leukemia patients and promotes abnormal proliferation and survival of myeloid cells in vitro and in vivo [7].

In spite of all the above findings, there is also evidence indicating that CREB1 could function as a tumor suppressor. In line with this idea, CREB1 has been shown to suppress AChE-R-induced, PKA-mediated proliferation of glioblastoma tumors [50]. It is interesting that CREB1 plays a pro-proliferative and anti-migratory role in glioma cells [29]. These data suggest that CREB1's role in human cancers is tissue- and/or cell type-specific, though it typically serves as a proto-oncogenic transcription factor.

CREB1 acts as a miRNA transcription activator

A precise control of miRNA levels is essential for maintaining normal cellular homeostasis and uncontrolled deregulation of miRNA may contribute to tumorigenesis. Interestingly, recent ChIP-seq (chromatin immunoprecipitation sequencing) data has provided evidence that CREB1 can bind to the promoter of several miRNAs in glioma cells and regulate their transcription [37]. In the following section, we will describe some of the verified or predicted CREB1-miRNA interactions in human cancers (Table 2, Fig. 1).

let-7i

Let-7i belongs to the let-7 family, which include 12 human homologues and are considered as tumor suppressors because they are frequently located at fragile sites and genomic regions involved in cancers [14]. Downregulation of let-7i has been correlated with tumor progression and anti-cancer drug resistance in many human malignancies [55–58]. Several groups have identified let-7i as a metastasis-specific miRNA biomarker associated with prognosis in colorectal cancer (CRC) and let-7i is validated to target TRIM41, SOX13, SLC25A4, SEMA4F, RPUSD2, PLEKHG6, CCND2, and BTBD3 in CRC cell lines [59, 60]. Recent evidence has also established let-7i as a transcriptional target of mutant p53 and repression of let-7i exhibits a key role in enhancing migration, invasion, and metastasis of human cancer [61]. Although let-7i plays an important role in various cancers, little is known about how let-7i expression is regulated. By means of bioinformatics-based analysis, Dai et al. find that let-7i is downregulated in apurinic/apyrimidinic endonuclease1 (APE1) knockdown human osteogenic sarcoma cells and contains two putative CREB1 binding sites in its promoter. This may indicate the potential function of CREB1 mediated by APE1 in the regulation of let-7i expression [51].

miR-9

MiR-9 has been reported to exert distinct and even opposite functions in different types of tumors through targeting different cellular genes. MiR-9 is upregulated in bladder cancer and promotes cell proliferation, cell cycle progression, invasion, and chemo-resistance, partly through directly downregulating LASS2 and CBX7 [62, 63]. Over-expression of miR-9 targets PPARA and CDH1 and induces HCC cell growth and invasiveness [64]. Cai et al. shows that high expression of miR-9 is correlated with aggressive clinic-pathological features and poor prognosis in HCC patients [65]. In contrast, Higashi and colleagues identify miR-9 as a tumor suppressor, which inhibits cell proliferation via targeting TAZ in HCC cells [66]. We suspect that different detection methods and specimens from different ethnic groups may account for the discrepancy. Recently, miR-9 is proved to inhibit the proliferation of glioma cells by inhibiting CREB1 expression [29]. Moreover, miR-9 is transcriptionally activated by CREB1, forming a negative feedback minicircuitry [29].

Table 1 Expression and function of CREB1 in human cancers

Cancer/cell types	CREB1 level	Sample size	Detection methods	Functions	Correlation with metastasis or prognosis	CREB1's targets	References
Astrocytoma	Upregulated	Astrocytomas ($n = 122$) v.s. non-neoplastic specimens ($n = 30$)	qRT-PCR	N.A.	Poor prognosis	N.A.	[31]
Breast cancer cells	Upregulated	Metastatic MDA-MB-231 v.s. non-metastatic MCF-7	WB	Increases proliferation, migration, invasion, and bone destruction	Promotes metastasis	PTHrP, MMPs, and OPG	[32]
Breast cancer tissues	Upregulated	Tumor ($n = 120$) v.s. non-neoplastic ($n = 33$)	IHC and qRT-PCR	N.A.	Metastasis and poor prognosis	N.A.	[33]
Breast cancer	N.A.	N.A.	N.A.	Transcriptional regulation of LAPTM4B	N.A.	LAPTM4B	[34]
Gastric cancer	N.A.	Cancer tissues ($n = 66$) v.s. normal gastric mucosa	IHC on TMA	Increases cell proliferation	N.A.	C/EBPbeta	[35]
Gastric cancer	Upregulated	Normal ($n = 50$) v.s. primary tumor ($n = 185$) v.s. metastatic foci ($n = 50$)	IHC	N.A.	Metastasis and poor prognosis	N.A.	[36]
Glioma cells	Upregulated	Glioma cell lines ($n = 4$) v.s. normal human glial cell line ($n = 1$)	qRT-PCR	Inhibits migration	N.A.	miR-9 and NF1	[29]
Glioma tissues	Upregulated	Glioma ($n = 15$) v.s. normal ($n = 2$)	WB and qRT-PCR	Increases growth and survival	N.A.	miR-23a	[37]
HCC	Upregulated	HCC ($n = 130$) v.s. non-neoplastic tissues ($n = 130$)	IHC and WB	N.A.	Poor prognosis	N.A.	[38]
Melanoma	N.A.	N.A.	N.A.	Promotes growth and metastasis	N.A.	CYR61	[39]
Meningioma	Upregulated	Meningiomas ($n = 70$) v.s. normal leptomeninges ($n = 10$)	IHC	N.A.	Angiogenesis, recurrence risk, and poor prognosis	N.A.	[40]
Mesothelioma	Upregulated	Mesothelioma sections ($n = 33$) v.s. normal lung sections ($n = 7$) v.s. reactive mesothelial hyperplasias ($n = 3$)	IHC on TMA	Increases migration and decreases apoptosis	N.A.	Bcl-2, c-FOS and MMP13, etc.	[41]
NSCLC cells	Upregulated	Four NSCLC cell lines v.s. NHTBE (normal) cells	WB	Increases growth and survival	N.A.	Bcl-2 and Bcl-xL	[42]
NSCLC tissues	Upregulated	Tumor ($n = 51$) v.s. normal ($n = 51$)	WB, PCR, and IHC	N.A.	Decreased overall survival	N.A.	[43]
Ovarian cancer	Upregulated	Serous adenocarcinoma ($n = 124$) v.s. mucous adenocarcinoma ($n = 25$) v.s. normal tissues ($n = 8$)	IHC on TMA	Promotes proliferation	Associated with tumor stage	N.A.	[44]
Prostate cancer	Upregulated	Normal/benign glands ($n = 5$) v.s. primary cancers ($n = 10$) v.s. bone metastatic tissues ($n = 7$)	IHC	Induces VEGF transcription	Bone metastasis	HIF-1a and VEGF	[45]
Prostate cancer	Upregulated	Cancer specimens ($n = 15$) v.s. normal prostate epithelium ($n = 15$)	IHC on TMA	Transcriptional regulation of cyclin D1	N.A.	Cyclin D1	[46]

HCC hepatocellular carcinoma, *NSCLC* non-small cell lung cancer, *qRT-PCR* quantitative real-time polymerase chain reaction, *IHC* immunohistochemistry, *WB* Western blot, *N.A.* not available or not associated, *TMA* tissue microarray

Table 2 CREB1-regulated miRNAs in human cancers

miRNA	Cancer/cell types	Validation methods of CREB1's regulation on miRNA	Regulation manner	miRNA alterations	Cell functions driven by miRNAs	Target genes of miRNA	References
let-7i	Osteogenic sarcoma	Bioinformatics analysis	Activation	Downregulated in APE1 knockdown cells	N.A.	APE1 and TLR4	[51]
miR-9	Glioma	Bioinformatics analysis, ChIP-qPCR, and qRT-PCR	Feedback loop	Upregulated in cancer	Inhibits growth but stimulates migration	CREB1 and NF1	[29]
miR-21	Breast and ovarian	Bioinformatics analysis, luciferase assay, and ChIP	Activation	N.A.	Promotes resistance to hypoxia and cell survival	PTEN, PDCD4, and Spry1	[52]
miR-23a	Glioma	MicroRNA microarray, ChIP-chip, and ChIP-qPCR	Activation	Upregulated in cancer	Increases growth and survival	FOXO3a and PTEN	[37]
miR-320a	Cervical	Bioinformatics analysis, qRT-PCR, luciferase assay, and ChIP	Activation	Upregulated in cancer	Promotes mitophagy	VDAC1	[53]
miR-335	HeLa cells	qRT-PCR and ChIP	Activation	Downregulated post irradiation	DNA repair, intra S-phase checkpoints, and radiosensitivity	CtIP	[54]
miR-373	Pancreatic	Luciferase assay, ChIP, and qRT-PCR	Activation	N.A.	Enhancement of cell proliferation, invasion, and tumor growth	TP53INP1, LATS2, and CD44	[30]

ChIP chromatin immunoprecipitation

miR-21

MiR-21 is over-expressed in most of the solid tumors. It regulates various cellular processes, such as cell cycle, proliferation, apoptosis, invasion, and drug resistance, by targeting multiple tumor suppressor genes [17, 67]. Recent studies have shown that miR-21 might be a biomarker for diagnosis and prognosis in cancer patients [21, 68]. One of the most important proof of miR-21's oncogenic activity may come from the Slack laboratory who showed that over-expression of miR-21 resulted in a pre-B cell lymphoma by a genetically engineered miR-21 mouse model. This experiment illustrates the significant impact of a single miRNA at all stages of in vivo tumor development: initiation, maintenance and survival [69]. As a mechanical study for upstream pathways of miR-21, Polytarchou et al. find that the miR-21 induction by Akt2 during hypoxia partially depends upon the binding of CREB1 to the miR-21 promoter [52]. Interestingly, miR-21 seems to be involved in a number of positive and negative feedback loops forming with transcription factors, and these complex regulations may explain why miR-21 is probably one of the most dynamic miRNAs responsive to various stimuli [70]. One evolutionary conserved double-negative feedback module is miR-21 and its direct target NFIB, a transcription factor involved in carcinogenesis [71].

miR-23a

MiR-23a belongs to the miR-23a-27a-24-2 cluster which locates in chromosome 19p13.12. It is among the most dysregulated miRNAs implicated in cancer. miR-23a, over-expressed in gastric cancer, has been reported to participate in the FasL-induced epithelial-mesenchymal transition (EMT) process [72] and confer poor prognosis in patients with gastric cancer [73]. Moreover, miR-23a is also demonstrated to stimulate TGF-beta-induced EMT by targeting E-cadherin [74], and promote the migration and invasion of A549 cells via its target IRS-1 [75] in lung cancer. Recently, miR-23a has been identified to repress the tumor suppressor PTEN and confirmed as a functional downstream target of CREB1 in controlling glioma cell growth and cell survival [37]. However, Cai et al. find that miR-23a is decreased in prostate cancer and inhibits cancer metastasis though the PAK6-LIMK1 pathway [76], suggesting a tissue- or cell-specific role of miR-23a in cancers.

miR-320a

MiR-320a, belonging to the miR-320 family (miR-320a~e), has been shown to be dysregulated in many human malignancies. MiR-320a typically functions as a tumor suppressive miRNA and has emerged as a key regulator of tumor initiation, progression, metastasis, as well as drug resistance.

Human miR-320a gene is localized at chromosome 8p21.3, which is frequently deleted during CRC progression and identified as a liver metastatic susceptibility locus [77, 78], thus miR-320a has been extensively investigated in CRC [60, 79–83]. Notably, miR-320a is found to be down-regulated in liver metastases tissues compared to matched primary CRC tissues [60, 81] and high expression of miR-320a is associated with better disease-free survival in CRC patients [84]. Functional studies have revealed that miR-320a decreases cell proliferation, migration, and invasion, induces G0/G1 growth arrest, and sensitizes chemoradiotherapy in CRC by targeting neuropilin 1, beta-catenin, and Rac1 [80–83]. Interestingly, miR-320a is identified as a direct target of transcriptional factor E2A and is involved in colon cancer cell growth [79]. In addition, miR-320a exerts its suppressive function by targeting BCR/ABL oncogene in chronic myeloid leukemia [85], BMI-1 in nasopharyngeal carcinoma [86], GNAI1 in hepatocellular carcinoma [87], IGF-1R in glioblastoma [88], ITGB3 in salivary adenoid cystic carcinoma [89], and ITGB3 in bladder cancer [90]. Intriguingly, CREB1 is found to activate miR-320a expression and induce mitophagy during serum starvation in cervical cancer cells and the CREB1-miR-320a-VDAC1 axis may provide new insights into cancer cell survival in response to environmental stresses [53].

miR-335

MiR-335 has been identified to be involved in tumorigenesis of numerous cancers such as ovarian cancer, lung cancer, HCC, prostate cancer, breast cancer, cervical cancer, neuroblastoma, pancreatic cancer, clear cell renal cell carcinoma, meningioma, glioma, esophageal squamous cell carcinoma, and gastric cancer [91–110]. The expression and function of miR-335 in different human cancers are highly dependent on the context or types of tumors. For example, Zhou [91] and Yang et al. [96] have demonstrated that the expression of miR-335 is significantly reduced in gastric cancer, and low expression of miR-335 is associated with aggressive clinical features and invasion and metastasis. However, miR-335 seems to be a tumor promoter in brain cancers including meningioma [105] and glioma [109]. Over-expressed miR-335 promotes cell proliferation and invasion by targeting Rb1 and PAX6 in meningioma and glioma, respectively. As to the regulation of CREB1 on miR-335, Martin et al. find that CREB1 could bind to the promoter region of miR-335 and induce miR-335 expression in HeLa cells [54]. They finally propose an ATM-dependent CREB-miR-335-CtIP axis that influences homologous recombination repair (HRR) of certain double-strand break (DSB) lesions.

miR-373

MiR-373 is located in the chromosomal band 19q13.4 and belongs to the miR-371-3 gene cluster (miR-371, miR-372, miR-373, and miR-373*) [111, 112]. MiR-373 was firstly identified as one of the human embryonic stem cell (ESC)-specific miRNAs [112]. Subsequently, it is proved to be an oncogene involving in the proliferation and tumorigenesis of human testicular germ cell tumors by numbing the p53 pathway [111]. Later, numerous studies have shown the pivotal roles of miR-373 in regulation of cell proliferation, apoptosis, senescence, migration, invasion, chemo-sensitivity, as well as DNA damage repair following hypoxia stress [113]. A recent study from Adi Harel et al. have revealed that miR-373 increases cisplatin-induced apoptosis and inhibits cell migration by targeting RelA and PIK3CA in lung cancer cells [114]. Intriguingly, miR-373 enhances cell proliferation, invasion, and tumor growth in pancreatic cancer and is transcriptionally activated by CREB1 through the regulation of miR-373's promoter [30].

CREB1 acts as a direct target of miRNA

MiRNAs regulate their targets by direct cleavage of the mRNA or by inhibition of protein synthesis, according to the degree of complementarities with their targets' 3′-UTR regions [20] and are thereby involved in the initiation and progression of human malignancies. As a key cancer-related pro-oncogenic gene, CREB1 has been predicted and validated to be direct targets of many miRNAs (Table 3, Fig. 1).

miR-17-92 cluster

MiR-17-92, a miRNA polycistron also known as oncomir-1, is among the most potent oncogenic miRNAs [124]. The miR-17-92 cluster is composed of seven miRNAs (miR-17-5p, miR-17-3p, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1) [115]. He et al. show that the miR-17-92 polycistron locating at 13q31-32 is upregulated in 65 % of the B cell lymphoma [125]. They also find miR-17-92 cluster acts together with MYC to accelerate tumor development [125]. The oncogenic role of the miR-17-92 cluster is further supported by profiling studies showing upregulation of this cluster in cancers and evidences indicating that miR-17-92 promotes proliferation, inhibits differentiation, increases angiogenesis, and sustains cell survival [124, 126]. Attar et al. show that miR-17-92 cluster over-expression in HEK-293 cells enhances cell proliferation and cell cycle-related genes, including CREB1, CDK2, cyclin-D2, and c-Myc, which were putative targets of miR-17-92.

Table 3 miRNAs directly target CREB1 in human cancers

miRNA	Cancer types	miRNA alterations in cancer	Validation methods of miRNA-CREB1 interaction	Regulation manner	Functions mediated by CREB1	Downstream effectors of CREB1	References
miR-9	Glioma	Upregulated	Luciferase assay and WB	Feedback loop	Enhances proliferation and inhibits migration	NF1	[29]
miR-17-92 cluster	HEK-293 T cells	N.A.	qRT-PCR and WB	Increase	Increases cell proliferation	N.A.	[115]
miR-27b/ miR-200b	Gastric	N.A.	Prediction algorithms, luciferase assay, qRT-PCR, and WB	Inhibition	N.A.	N.A.	[36]
miR-34b	Acute myeloid leukemia	Downregulated	Luciferase assay and WB	Inhibition	Increases cell proliferation and clonogenicity	Cyclin A1, cyclin B1, cyclin D1, BCL-2, STAT3, JAK1, NF-κB, etc.	[116, 117]
miR-181b	Gastric	Downregulated	Fluorescent reporter assay, WB, qRT-PCR, and rescue experiments	Inhibition	Increases cell growth	N.A.	[118]
miR-182	Gastric	Downregulated	Fluorescent reporter assay, WB, qRT-PCR, and rescue experiments	Inhibition	Increases cell growth	N.A.	[49]
miR-200b	Glioma	Downregulated	Prediction algorithms, luciferase assay, qRT-PCR, WB, and rescue experiments	Inhibition	Increases cell growth	N.A.	[31, 119]
miR-203	Melanoma	Hypermethylation/ downregulated	Bioinformatics algorithms, luciferase reporter assay, and WB	Inhibition	Increases cell proliferation	MITF and RAB27a	[120–122]
miR-433	HCC	Hypermethylated	Bioinformatics algorithms, luciferase reporter assay, WB, and rescue experiments	Inhibition	Increases cell proliferation, migration, and invasion	N.A.	[123]

miR-27b

As a member of the miR-23b/27b cluster, miR-27b is frequently downregulated in various types of human cancers [127]. Expression of miR-27b is significantly reduced in prostate cancer, especially in metastatic, castration-resistant tumors [128, 129]. MiR-27b significantly inhibits cell proliferation, migration, and invasion in prostate cancer cells by targeting GOLM1 [128] and Rac1 [129]. Similarly, miR-27b-mediated suppression of Sp1 [130] and LIMK1 [131] attenuate the growth and invasion of NSCLC cells. miR-27b has also been reported to enhance drug response by activating p53-dependent apoptosis and reducing CYP1B1-mediated drug detoxification in liver and kidney cancers [132]. However, miR-27b may act as a pro-oncogenic player in several tumors, such as HPV-associated cervical cancer [133], glioma [134], and breast cancer [126, 135]. In addition, we and other groups have identified CREB1 as direct target of miR-27b in gastric carcinogenesis [36] and adipogenesis [136]. In our previous study, we identified CREB1 as a novel target of miR-27b in gastric cancer [36]. However, our recent work suggested a positive correlation between CREB1 and miR-27b in gastric cancer tissues (Online Resource Figure S1A), which were counter to the proposed inverse relationship between miR-27b and its target CREB1. One possible explanation is that CREB1 may act as a transcriptional activator to induce miR-27b expression. To support this hypothesis, we utilized miRStart [137], a source of human microRNA TSSs (transcription start sites, http://mirstart.mbc.nctu.edu.tw/home.php), to get the putative TSSs and promoter sequences of miR-27b. Then, we used RegRNA2.0 [138] and PROMO database [139] to predict potential binding sites for CREB1. The analysis revealed the presence of several CREB1-binding sites in the putative promoter of miR-27b (Figure S1B, C). However, further experiments are needed to validate the relationship between CREB1 and miR-27b.

miR-34b

MiR-34b belongs to the evolutionary conserved miRNA family miR-34s [140], which are known to be the transcriptional targets of tumor suppressor p53 [141] and are regulated by DNA hypermethylation [142]. MiR-34b has been implicated in the oncogenesis of colon [143], ovarian [144], prostate [145, 146], hepatocellular [147], lung [148], pancreatic [149], breast [150], and oral cancers [151]. MiR-34b is prevailingly identified as an important component of the tumor suppressor network during carcinogenesis; however, increased miR-34b is observed by Hiyoshi et al. in advanced colon tumors and is associated with poor survival of cancer patients [142]. Pigazzi et al. find that miR-34b directly target CREB1 in acute myeloid leukemia (AML) [116]. MiR-34b expression can cause cell cycle abnormalities, reduce anchorage-independent growth, and alter CREB1 target gene expression in AML [116]. Interestingly, FOXO3a is transcriptionally responsible for miR-34b expression in breast cancer [150], further supporting the transcription factor-miR-34b interaction in human cancers.

miR-181b

MiR-181 family members contain four highly conserved mature miRNAs (miR-181a, miR-181b, miR-181c, and miR-181d) [152], which have been reported to contribute to tumor initiation and progression. Liu et al. briefly summarize the functional significance and clinical implications of miR-181b in cancer [153]. They propose that miR-181b is a critical link between inflammation and cancer, supported by the evidence that miR-181b inhibits CYLD to increase NF-kappaB activity, which is required for maintaining the transformed state [154] and regulating NF-kappaB-mediated vascular inflammation [155]. MiR-181b is over-expressed in ovarian [156], pancreatic [157], head and neck [158], and bladder cancers [159]. By contrast, miR-181b is downregulated in thyroid papillary cancer [160], glioma [161, 162], astrocytoma [163], acute myeloid leukemia [164], and prostate cancer [165]. MiR-181b is a key regulator of the oncogenic process involving cellular growth, apoptosis, invasion, metastasis, and drug sensitivity. Controversial evidence is observed by two research group reporting inconsistent expression and function of miR-181b in gastric cancers [118, 166]. Tang et al. indicates that miR-181b may function as a tumor suppressor in gastric cancer cells through directly targeting CREB1 [118]. However, Guo et al. suggests that miR-181b is over-expressed in gastric cancer cells and tissues and targets TIMP3 to increase cell proliferation, migration, and invasion [166]. Both of the two studies include relatively small sample size (10 to 12 pairs of gastric tissues) and meanwhile lack in vivo confirmation. We thus suggest that further studies are needed to validate the roles of miR-181b in gastric cancer.

miR-182

MiR-182, a member of the evolutionarily conserved miR-183-96-182 cluster, has been demonstrated to play important roles in a variety of cancers [167]. MiR-182 is upregulated in most types of tumors [168] and participate in apoptosis, growth, differentiation, metastasis and chemo-sensitivity of cancer cells [169–176]. For example, CEBPA and RASA1 targeting miR-182 has been shown to be upregulated and promote angiogenesis in HCC [171, 177]. By comparing the expression of miRNAs in metastatic and non-metastatic primary mouse sarcomas, Sachdeva et al. find that miR-182 is over-expressed in tumors metastasized to the lungs [172]. MiR-182 is identified as a metastasis driver of primary

sarcomas by targeting multiple genes [172]. However, reports on the expression and function of miR-182 in gastric cancer are controversial [167]. Kong [49] and Tang et al. [178] find that miR-182 is downregulated in gastric carcinoma and inhibits proliferation through targeting oncogenic CREB1 and ANUBL1. Li et al. report that miR-182 is upregulated in intestinal-type gastric cancers and increases along with tumor stage [179]. Similar to miR-181b, larger samples and in vivo assays may be useful to further elucidate the exact roles of miR-182 in gastric cancer.

miR-200b

Members of the miR-200 miRNA family (miR-200a, miR-200b, miR-200c, miR-141, and miR-429) are mainly downregulated in human cancer cells and tissues and play a crucial role in the suppression of EMT, tumor cell adhesion, migration, invasion, metastasis, and cancer chemo-sensitivity [19, 180, 181]. MiR-200b is found to be lost in invasive breast cancer cell lines with mesenchymal phenotype and prevent TGF-beta-induced EMT and tumor metastasis, by targeting the E-cadherin transcriptional repressors ZEB1 and ZEB2 [182]. Additionally, ZEB1 and ZEB2 have been found to bind directly to an E-box proximal minimal promoter element and repress miR-200b expression in mesenchymal human breast cancer cells, demonstrating a potential double-negative feedback loop between ZEB1/ZEB2 and miR-200b during EMT and tumorigenesis [183]. More recently, Wu et al. have also reported a negative feedback loop between miR-200b and the NF-kappaB pathway via IKBKB/IKK-beta in breast cancer cells [184]. They demonstrate that miR-200b, a transcriptional target of NF-kappaB, suppresses breast cancer cell growth and migration as well as NF-kappaB activation through the downregulation of IKBKB. Interestingly, the transcription factor CREB1 is proved to be a direct target of miR-200b in glioma [119] and gastric cancer [36]. Whether there exists a feedback loop between transcription factor CREB1 and miR-200b warrants further investigation.

miR-203

MiR-203 has been reported to be a tumor suppressor and EMT-associated miRNA which is silenced in different malignancies. It is reported that miR-203 inhibits cell proliferation, adhesion, migration, invasion, metastasis as well as enhances chemo-sensitivity in cancer cells [120, 185–188]. MiR-203 suppression in gastric cancer promotes Slug-mediated cancer metastasis [189]. Similarly, miR-203 acts as a growth-suppressive miRNA in *Helicobacter pylori*-related gastric cancer by repressing CASK expression [186]. A retrospective study by Imaoka et al. shows that low serum miR-203 expression is an independent predictive marker for lymph node, peritoneal, and distant metastases and associates with poor prognosis in patients with gastric cancer [185]. MiR-203 suppresses the proliferation, migration, and invasion and promotes the apoptosis of lung cancer cells by targeting Bmi1, FZD2, and SRC [190–192]. MiR-203 enhances 5-FU chemo-sensitivity via downregulating TYMS in CRC [193] and attenuates cell proliferation, invasion, and migration by suppressing ZNF217 [194]. MiR-203 is a tumor suppressor miRNA inhibiting cellular proliferation by directly targeting CREB1 [121] and regulating its downstream targets, MITF and RAB27a [120, 122] in melanoma cells.

miR-433

For the last decade, extensive research has identified the pivotal role of miR-433 in human cancers, including ovarian cancer [195, 196], gastric cancer [197], myeloproliferative neoplasms [198], lung cancer [199], and HCC [123]. Expression of miR-433 is downregulated in gastric carcinoma [200–202], which is associated with unfavorable overall survival [197]. MiR-433 inhibits gastric cancer cell proliferation, cell cycle progression, cell migration and invasion by directly interacting with oncogenic KRAS [202] and tumor-associated protein GRB2 [200]. MiR-433 is aberrantly expressed in myeloproliferative neoplasms and suppresses hematopoietic cell growth and differentiation by negatively regulating GBP2 [198]. High expression of miR-433 is associated with poor progression-free survival in patients with high-grade serous ovarian cancer and promotes resistance to paclitaxel through the induction of cellular senescence in ovarian cancer cells [195]. Yang et al. demonstrates that miR-433 inhibits HCC cell migration by repressing the protein expression and function of CREB1 [123].

Conclusions and perspectives

In this review, we briefly summarize the bidirectional interactions between CREB1 and miRNA in human cancers (Fig. 1). We believe that, except for miR-9, other single miRNA may also form a negative feedback loop with CREB1, which deserves further investigation. Both CREB1 and miRNA have been shown to regulate important cancer hallmarks, including proliferation, apoptosis, metastasis, and drug resistance. A recent integrative analysis of gene and miRNA expression profiles with transcription factor-miRNA feed-forward loops identifies CREB1 and its miRNA partners as master regulators across multiple cancer types [203]. Given its critical roles in cancer development and progression, the CREB1-miRNA network (Fig. 1) may represent novel therapeutic targets in human cancers. This network includes the important node—CREB1 itself, the miRNAs (e.g., miR-34b, miR-200b)

severing as upstream regulators of CREB1, and the CREB1 target coding genes (e.g., cyclin D1, BCL-2) and miRNAs (e.g., miR-23a, miR-373). On one hand, miRNA target prediction and validation, including the bioinformatic databases [204], have gain remarkable advances in recent years. We comprehensively searched four databases of experimentally validated miRNA target interactions (miRWalk 2.0, miRTarBase, miRecords, and TarBase 7.0) and found that nearly 100 miRNAs could potentially target CREB1 in human species. Although not all information in these databases are up-to-date or accurate, which need further improvement (see comments of Dweep H and Kenneth Witwer that appeared in PubMed Commons of [205]), they are still useful tools to find putative miRNA targets in the discovery stage of investigations. On the other hand, as more and more miRNAs are proved to be targets of transcription factor CREB1, we comment that in the future, CREB1 ChIP assays in combination with miRNA sequencing should be helpful to identity novel target miRNAs of CREB1. By fully understanding the regulatory networks of CREB1 and miRNA, we could be able to evaluate the potential of CREB1 and miRNA as therapeutic targets in human cancers.

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Compliance with ethical standards

Conflicts of interest None

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