Controversial roles of cold-inducible RNA-binding protein in human cancer (Review)

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Abstract. Cold-inducible RNA-binding protein (CIRBP) is a cold-shock protein comprised of an RNA-binding motif that is induced by several stressors, such as cold shock, UV radiation, nutrient deprivation, reactive oxygen species and hypoxia. CIRBP can modulate post-transcriptional regulation of target mRNA, which is required to control DNA repair, circadian rhythms, cell growth, telomere integrity and cardiac physiology. In addition, the crucial function of CIRBP in various human diseases, including cancers and inflammatory disease, has been reported. Although CIRBP is primarily considered to be an oncogene, it may also serve a role in tumor suppression. In the present study, the controversial roles of CIRBP in various human cancers is summarized, with a focus on the interconnectivity between CIRBP and its target mRNAs involved in tumorigenesis. CIRBP may represent an important prognostic marker and therapeutic target for cancer therapy.

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1. Introduction

Cold-inducible RNA-binding protein (CIRBP; also called CIRP and hnRNP A18) was identified as a cold-shock protein and an RNA-binding protein (RBP) expressed following a variety of stressors, such as hypoxia, cold shock and UV radiation (1-3). In total, two major CRIBP transcripts are expressed in cells through N^6-methyladenosine modification-mediated alternative splicing (2,4-6). The large isoform of CIRBP (CIRBP-L) contains 297 amino acids and another short one (CIRBP-S) encodes 172 amino acids (Fig. 1). CIRBP is translated in the nucleus and migrates to the cytoplasm following stimulation (1,7). CIRBP contains an RNA-recognition motif (RRM) in the N-terminal domain and an arginine-rich motif (RGG) in the C-terminal region (1); it interacts with the 5' or 3'-UTR of partner mRNAs through its RRM and regulates its expression post-transcriptionally (1,8). The RGG domain of CIRBP induces the protein-protein interaction, thereby modulating the protein-RNA interaction. Therefore, it is likely that CIRBP acts as a chaperone protein to interact and support RNA structure, assembly and transport of various proteins (9).

Moreover, CIRBP participates in multiple cellular signaling pathways as a crucial regulator. In the apoptosis pathway, mild hypothermia can protect cells from death in part through CIRBP, which activates the MAPK and NF-κB pathways (3). This indicates that CIRBP functions as a regulator of cell viability by activating survival signaling. Under mild hypothermia and UV radiation, CIRBP upregulates the expression of thioredoxin (TRX), which protects cells from oxidative damage by sequestering reactive oxygen species (ROS) (10,11). These findings indicate that CIRBP can induce anti-senescence signaling through TRX-mediated antioxidant activity. In addition, CIRBP is involved in various biological processes, including DNA repair, circadian clock regulation, telomere integrity, nutrient deficiency, inflammatory response signaling and cardiac electrophysiology (12-18). Furthermore, CIRBP is also involved in various human diseases, including sepsis, Alzheimer's disease and pancreatitis (19-24).

In recent years, numerous studies have suggested the involvement of CIRBP in several forms of human cancer. In the present review, the roles of CIRBP and its target mRNAs in cancer are summarized, and its potential as a therapeutic target is evaluated.

2. Controversial roles of CIRBP in regulating hallmarks of cancer

RBPs not only serve important roles in multiple physiological signaling pathways, but also act as important regulators of cancer genesis and progression. Several studies have reported that RBPs influence cancer progression by acting as either oncogenes or tumor suppressors (25,26). In order for normal cells to develop into cancer cells, they must go through a multi-step process to acquire the hallmarks of cancer. Hallmarks of cancer have been previously described and updated with newly identified characteristics of cancer (27). In the present review, the role of CIRBP in human cancers was summarized based on the hallmarks of cancer. Similar to other RBPs, CIRBP has a promotive or inhibitory regulatory effect on carcinogenesis, depending on the cancer subtype (Table I).

CIRBP in proliferative signaling. The most fundamental characteristic of cancer cells is the capacity to maintain unlimited proliferation. Healthy tissues maintain structure and function by carefully regulating cell growth to ensure cell number homeostasis, whereas cancer cells exhibit excessive proliferation (28). CIRBP significantly promotes the proliferation of breast and bladder cancer cells (29,30). Recently, it has been reported that CIRBP expression is elevated in luminal breast cancer, promoting cell proliferation and clonogenicity (31). Notably, CIRBP levels are closely associated with a less favorable survival rate in patients with the luminal subtype (31). Moreover, CIRBP enhances the proliferation of immature male germ cells through its interaction with dual-specificity tyrosine-phosphorylation-regulated kinase 1B (DYRK1B) in mice (32).

In addition to its role in carcinoma, CIRBP expression is also increased in pituitary corticotroph adenoma, which promotes cell proliferation and tumor growth via Erk signaling (33). However, certain reports have revealed that CIRBP can suppress the tumorigenesis of breast cancer cells (34,35). High expression of CIRBP in breast tissue has been correlated with a more favorable prognosis in postmenopausal women with breast cancer who have experienced childbirth (34). Another study also reported that CIRBP overexpression interferes with cell proliferation during mammary gland development (35). In addition, CIRBP expression is highest in normal endometrium, but significantly reduced in endometrial carcinoma (36). Recently, CIRBP was also reported to induce translation of p27, a CDK inhibitor, thereby reducing cell proliferation (37).

CIRBP in replicative immortality. Telomeres are essential for genome stability, as they protect the fusion of linear chromosomes (38). Telomeres are extended and maintained by telomerase, which is comprised of telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC). Although it is virtually silent in somatic cells, TERT expression is activated in numerous tumor types, giving cancer cells the hallmark feature of replicative immortality (39). For the maintenance of telomere length, CIRBP has been identified as a telomerase-associating protein through its RRG domain (40). Upon direct interaction with TERC, CIRBP promotes the formation of the telomerase complex. In addition, CIRBP enhances the telomerase activity through stabilization of TERT mRNA. As activated TERT is a common trait in most cancer types, this may represent an important approach to understanding the exact role of CIRBP in the regulation of telomerase activity.

CIRBP in the cell death pathway. Apoptosis acts as a natural barrier to tumorigenesis and is suppressed in tumors that have successfully progressed to a treatment-resistant state (41). Previous studies have reported an association between CIRBP and apoptosis. For example, CIRBP-overexpressing cells have a reduced rate of apoptosis owing to reduced DNA damage (42,43). A recent study reported that CIRBP inhibits amyloid β-induced activation of apoptosis via anti-oxidative pathways in cortical neurons (44). Notably, CIRBP stimulates NLRP3 inflammasome activation and simultaneously induces caspase-1 activation and IL-1β release, resulting in pyroptosis, a type of inflammatory cell death (45). Additionally, cancer cells must evade pathways involving tumor suppressor genes, such as p53 and retinoblastoma protein, which negatively regulate proliferation (46). It has been reported that CIRBP inhibits p53, thereby reducing apoptosis (42) and suppressing the damage of testicular tissue (47), but the exact mechanism is still unknown.

CIRBP in tumor-promoting inflammation. Cancer cells use the inflammatory microenvironment to promote tumor growth. Tumor-promoting inflammation is closely associated with tumor progression and metastasis (48). Certain studies have reported that CIRBP acts as a mediator of cancer-associated inflammation in numerous cancer types. Chronic inflammation is known to increase the risk of intestinal cancer in patients with inflammatory bowel disease (IBD) (49). In patients with IBD, CIRBP is positively correlated with IL-23A (50), a known oncogenic cytokine, and IL-17, which is known to enhance cancer-induced inflammation (51,52). Moreover, CIRBP expression is higher in inflammatory cells compared with epithelial cells in patients with IBD, and the same result is observed in patients with colitis-associated colorectal cancer (CAC) (52). In another study, CIRBP deficiency resulted in decreased expression of inflammatory cytokines in liver-specific macrophages and attenuated tumorigenesis in mice (53). Oral chronic inflammation is a crucial part of oral squamous cell carcinoma (OSCC) promotion (54). The expression of CIRBP and toll-like receptor 4 (TLR4) is high, and a positive correlation in their expression levels has been reported in patients with OSCC (55). In a previous study, it was reported that CIRBP induced an inflammatory response through TLR4 (15). Overall, these findings indicate that CIRBP can modulate the development of cancer through the regulation of the inflammatory response.

CIRBP in invasion and metastasis. A major characteristic that distinguishes cancer cells from normal cells is their ability to spread through invasion and metastasis. Metastasis is the major cause of cancer-related mortality in patients. In addition to the previously mentioned role of CIRBP in proliferative signaling, several studies have reported that CIRBP is involved in the metastasis of multiple cancer types (56,57). CIRBP is upregulated in 57% of human bladder cancer tissues and cancer cell lines, and it is reported to enhance migration and metastasis *in vivo* and *in vitro* (29). Breast cancer is one of the leading causes of cancer-associated mortality in women (58). Notably,

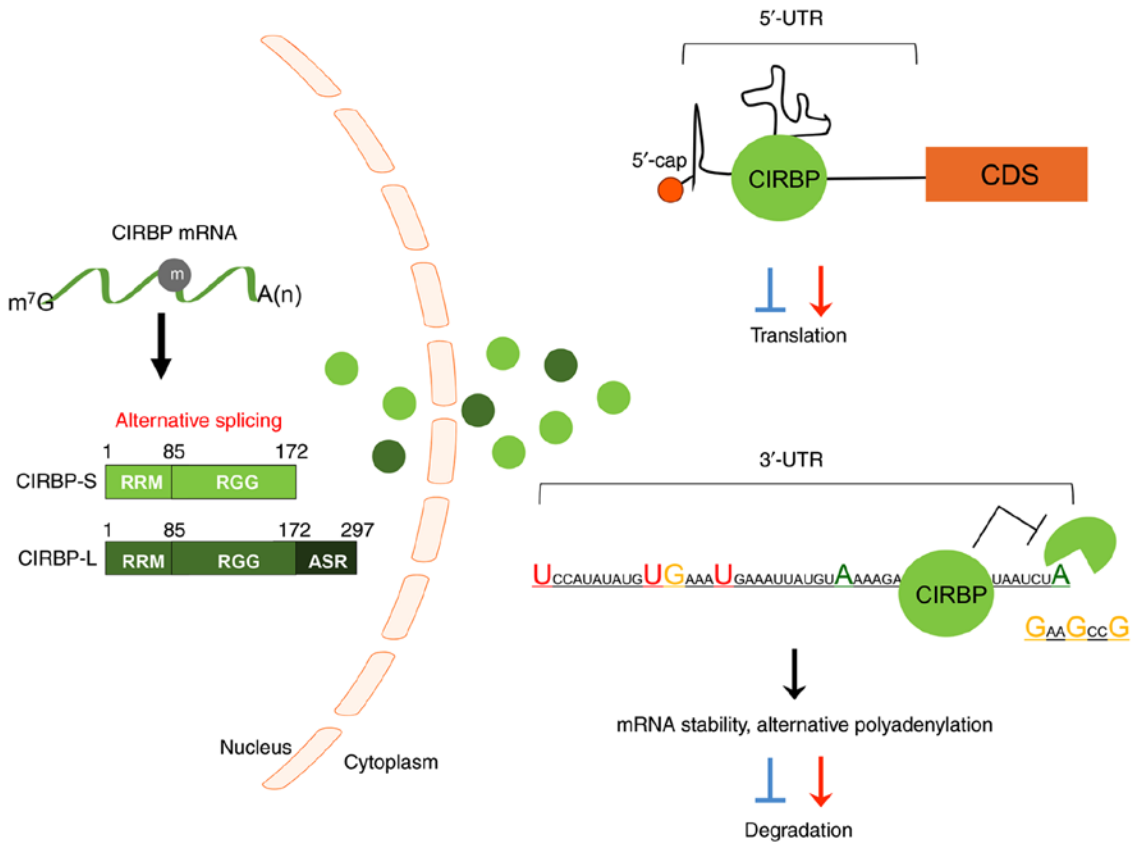

Figure 1. Regulation of target RNAs by CIRBP. N^6-methyladenosine modification in the exon sequence promotes the alternative splicing of CIRBP mRNA. Consequently, two isoforms of CIRBP are formed (both containing RRM and RGG motifs). CIRBP-S encodes 172 amino acids, while CIRBP-L has 297 amino acids and also contains an ASR motif. CIRBP translocates to the cytoplasm and binds the 5'-UTR of target mRNA to regulate translation. CIRBP also regulates mRNA stability and polyadenylation by binding to the glycine rich region and other consensus sequences located in the 3'-UTR of target mRNA, thereby affecting translation. ASR, alternatively spliced region; CDS, coding sequence; CIRBP, cold-inducible RNA-binding protein; L, long isoform; m^6A, N^6-methyladenosine; RRM, RNA-recognition motif; S, short isoform; UTR, untranslated region.

progressive breast cancer is virtually incurable and the cause of a high mortality rate in patients. CIRBP downregulation was shown to reduce the invasion and migration capacity of breast cancer cells, and CIRBP upregulation was observed in more aggressive breast cancer subtypes compared with ductal carcinoma, *in situ* (30). Moreover, CIRBP exhibited strong metastasis-promoting activity in invasive ductal carcinoma (59) and invasive brain metastases (60). In addition, epithelial-mesenchymal transition (EMT) is a crucial process for cancers metastasizing from the original site to other organs (61). During TGF-β-induced EMT, CIRBP silencing was shown to inhibit the upregulation of the master regulator, Snail, thereby suppressing the migration of hepatocellular carcinoma cells (62). This indicates that CIRBP is involved in metastasis of HCC and, therefore, the low survival rate of patients with HCC. However, in contrast to its oncogenic role in certain cancer types, several studies have shown that CIRBP can suppress cancer metastasis (56,63). CIRBP is negatively correlated with distant metastasis in nasopharyngeal cancer (56), and is downregulated in patients with aggressive metastatic TNBC (63).

CIRBP in angiogenesis. Angiogenesis is regulated by chemical signals such as VEGF, which binds to endothelial cell receptors and initiates intracellular signaling to promote the growth of new blood vessels (64). Neoangiogenesis represents an important step in cancer and is required to supply nutrients and oxygen to the tumoral cells, and to remove the waste products (65). Melanoma tumors with decreased CIRBP expression exhibit specifically downregulated VEGF expression compared with controls when using the angiogenesis proteome profiler array (30). Conversely, strong staining of CD31, an angiogenesis marker, was observed in a skin wound-healing sample of CIRBP-knockout mice compared with wild-type mice (66). Moreover, a recent study demonstrated that knockdown of CIRBP enhances the regeneration of ischemic muscle tissues, damaged by unilateral ligation of the hindlimb femoral artery, through acceleration of angiogenesis and M2-like macrophage polarization (67). These studies strongly indicate that CIRBP serves a role in angiogenesis, which may modulate tumor growth.

3. Molecular mechanism of CIRBP for regulating target RNAs

CIRBP is commonly overexpressed in a number of cancer tissues and cell lines. It acts as an oncogene by increasing the stability and translation of cancer-associated mRNA targets. However, several studies have also suggested the potential of CIRBP as a tumor suppressor by modulating the stability of target mRNAs (Fig. 1; Table II). CIRBP can bind the 5' and 3'-UTRs of mRNAs, as well as poly U sequences at the 3'-ends (68). It has been suggested that its

Table I. Expression and controversial roles of CIRBP in human cancers.

First author(s), year	Cancer type	Experimental method	Expression in cancer	Role of CIRBP in cancer	Cohort/cell line	(Refs.)
Guo *et al*, 2010	Breast	RT-qPCR and western blotting	Upregulated	Promoting proliferation and decreasing apoptosis	Breast cancer cells	(69)
Chang *et al*, 2016	Breast	IHC	Upregulated	Promoting proliferation, migration and invasion	91 TMA samples	(30)
Indacochea *et al*, 2021	Breast	Western blotting	Upregulated	Promoting proliferation	Breast cancer cells	(31)
Chang *et al*, 2016	Melanoma	IHC and western blotting	Upregulated	Promoting migration and invasion	77 TMA samples; melanoma cells	(30)
Biade *et al*, 2006	Ovarian	Microarray and RT-qPCR	Downregulated	Reducing cell doubling time	86 specimens	(81)
Artero-Castro *et al*, 2009	Colon	Western blotting and RT-qPCR	Upregulated	Promoting proliferation	31 patients	(73)
Sakurai *et al*, 2015	Liver	IHC	Upregulated	Increasing HCC recurrence	12 patients who underwent hepatectomy	(53)
Lu *et al*, 2018	Bladder	IF and western blotting	Upregulated	Promoting proliferation and migration	Bladder cancer and paracancerous tissue samples (n=20); bladder cancer cells	(29)
Hamid *et al*, 2003	Endometrial carcinoma	IHC and western blotting	Downregulated	Decreasing proliferation	Endometrial carcinomas (n-39); normal endometria (n=27)	(36)
Lin *et al*, 2019	Nasopharyngeal carcinoma	IHC, RT-qPCR and GEO dataset	Downregulated	Decreasing proliferation	NP and NPC samples; GSE53819, GSE12452 and GSE13597	(56)

CIRBP, cold-inducible RNA-binding protein; GEO, Gene Expression Omnibus; HCC, hepatocellular carcinoma; IF, immunofluorescence; IHC, immunohistochemistry; NP, nasopharyngeal epithelial tissues; NPC, nasopharyngeal cancer; RT-qPCR, reverse transcription-quantitative PCR; TMA, tissue microarray.

binding is important for the translation of interacting mRNAs by regulating polyadenylation and 3'-end cleavage (7,37). In the context of stress-induced regulation, abnormal upregulation of CIRBP promotes hypoxia inducible factor (HIF)-1α expression (29). Due to stabilization of the HIF-1α mRNA transcript, increased HIF-1α can bind to the promoter region of prostaglandin I2 synthase, a tumor suppressor, resulting in its downregulation (29) and an increase in the growth and invasion of cancer cells. An *in vitro* study demonstrated that CIRBP can also increase the mRNA stability of cyclin E1 in breast cancer (69). Responding to DNA damage, CIRBP can bind to the 3'-UTRs of TRX, replication protein A2 and ATR serine/threonine kinase mRNAs and increase their translational efficiencies (7,10,70). A recent study reported that, in luminal breast cancer, CIRBP is upregulated and enhances oncogenic properties by downregulating the CST3 mRNA expression levels (31). Notably, CIRBP can also enhance telomere maintenance by upregulating TERT mRNA levels (40). In most human cancer cells, active telomerase is upregulated, highlighting the importance of TERT expression and telomerase activity in promoting cancer progression (71,72). Other CIRBP-mediated regulatory effects have also been reported in human cancers. For example, CIRBP can increase phosphorylation of ribosomal protein S6, and eukaryotic translation initiation factor 4E-binding protein1, a protein that regulates the elongation phases of translation (73). In addition, CIRBP can promote cell proliferation by upregulating cyclin D1 and downregulating p27 via ERK signaling (33). Within the MAPK pathway, ERK signaling is involved in various human diseases, including inflammatory-related diseases and cancer (74,75). Additionally, CIRBP reduces phosphorylation of p27 by interacting with DYRK1B and inhibiting its

Table II. Target mRNAs of CIRBP.

Author, year	Target mRNA	Binding site	Regulation of CIRBP for target mRNA	Biological roles of target mRNA	Cell lines	(Refs.)
Guo *et al*, 2010	Cyclin E1	3'-UTR and CDS	Stabilization of the transcript	Regulating G_1/S phase transition	Breast cancer cells	(69)
Lu *et al*, 2018	HIF-1α	3'-UTR	Stabilization of the transcript	Response to hypoxia	Bladder cancer cells	(29)
Chang *et al*, 2016	TRX	3'-UTR	Stabilization of the transcript	Cellular redox metabolism	Melanoma cells	(30)
Chang *et al*, 2016	ATR and RPA2	3'-UTR	Stabilization of the transcript	DNA repair	Breast cancer cells	(30)
Zhang *et al*, 2016	TERT	3'-UTR	Stabilization of the transcript	Telomerase components	Uterus, cervix cells	(40)
Morf *et al*, 2012	CLOCK	3'-UTR	Stabilization of the transcript	Circadian gene	Fibroblasts	(13)
Roilo *et al*, 2018	p27	5'-UTR	Increasing translation	Cyclin-dependent kinase inhibitor	Breast cancer cells	(37)
Indacochea *et al*, 2021	CST3	Unknown	Decreasing translation	Tumor suppressor	Breast cancer cells	(31)
Jian *et al*, 2016	Cyclin D1	Unknown	Increasing translation	Regulating G_1/S phase transition	Pituitary corticotroph cells	(33)
	p27	Unknown	Decreasing translation	Cyclin-dependent kinase inhibitor		
Artero-Castro *et al*, 2009	S6 and 4E-BP1	Unknown	Increasing translation	Initiation and elongation phases of translation	MEFs	(73)

4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; ATR, ATR serine/threonine kinase; CDS, coding sequence; CIRBP, cold-inducible RNA-binding protein; CST3, cystatin C; HIF-1α, hypoxia inducible factor-1α; MEF, mouse embryonic fibroblast; RPA2, replication protein A2; TERT, telomerase reverse transcriptase; TRX, thioredoxin; UTR, untranslated region; CLOCK, clock circadian regulator.

binding to p27 in mouse germ cells (32). CIRBP also interferes with the phosphorylation of cyclin D1 by DYRK1B, thereby stabilizing cyclin D1 and ultimately increasing proliferation (32). Conversely, another study showed that CIRBP had an anti-proliferative function by binding to the 5'-UTR of p27 and increasing p27 expression in mouse embryonic fibroblasts (37).

The association between cancer and inflammation has been reported in numerous studies. In chronic airway inflammation disease, CIRBP upregulates mucin-5AC, which is associated with pulmonary disease via NF-κB/TLR4 signaling (76). In a CAC mouse model, CIRBP depletion reduced the level of inflammation markers, such as TNF-α and IL-23, and consequently decreased the susceptibility to CAC development (52). CIRBP can induce ROS accumulation by increasing the expression of inflammatory cytokines (IL-6 and IL-1β) in liver-specific macrophages. Conversely, CIRBP-knockout mice exhibited a decreased level of inflammatory cytokines with attenuated ROS accumulation (53). Together, these studies suggest that CIRBP may function as a tumor promoter or tumor suppressor by modulating the expression of inflammatory mediators.

4. CIRBP as a prognostic marker in cancer

Applicable prognostic cancer biomarkers in cancer are crucial for better tumor prediction and treatment planning. Several studies have shown the potential of RBPs as prognostic markers for various types of cancer, such as gastric or breast cancer (77,78). Consequently, databases such as TCGA (https://portal.gdc.cancer.gov/) and GEO (https://www.ncbi.nlm.nih.gov/geo/) containing the expression level of CIRBP in samples from patients with cancer were selected, and the potential of CIRBP as a prognostic marker in human cancers was presented (Table III).

A recent study indicated that CIRBP is methylated in the plasma of non-small cell lung carcinoma (NSCLC) with occult lymph node metastasis. RNA sequencing data obtained from The Cancer Genome Atlas (TCGA) also revealed that the mRNA expression levels of CIRBP are higher in metastatic tissues compared with primary breast tumor samples (79). Similar to previous RNA sequencing data, CIRBP is upregulated in invasive ductal carcinoma (59) and in patient with brain metastases with a high recurrence rate (60). These studies suggest that

Table III. CIRBP as a prognostic biomarker in human cancer.

Author, year	Cancer type	Type of evidence	Statistics	Cutoff point for prognosis	(Refs.)
He and Zuo, 2019	NSCLC	Cox analysis of 1,331 early-stage NSCLC specimens (TCGA and GEO)	GSE31210: HR, 0.25 (CI, 0.13-0.48), $P=3x10^{-5}$; GSE37745: HR, 0.65 (CI, 0.45-095), $P=2.7x10^{-2}$; GSE50081: HR, 0.6 (CI, 0.39-0.96), $P=2.3x10^{-2}$; TCGA: HR, 0.67 (CI, 0.53-0.85), $P=8.4x10^{-4}$	Cox regression analysis; HR<1 and P<0.05; good prognosis	(80)
Chen *et al*, 2020	NSCLC	Methylation sequencing of 119 patients with NSCLC with or without LN metastasis	AUC of the LN metastasis: 88.6% (95% CI, 87.8-89.4) in plasma samples and 74.9% (95% CI, 72.2-77.6) in tissue samples of malignant lung nodules	FDR cutoff <0.2; poor prognosis	(57)
Ren *et al*, 2014	OSCC	IHC of 61 specimens from patients with OSCC	T stage, P=0.028; Clinical stage, P=0.002; Histological classification, P=0.022; Lymph node metastasis, P=0.033	Univariate analysis; P<0.05; poor prognosis	(55)
Biade *et al*, 2006	Ovarian cancer	Microarray of benign (n=29), borderline (n=34) and malignant (n=57) ovarian tumor specimens	PAM Score: Benign, 0.2298; Malignant, 0	PAM score>0; good prognosis	(81)
Lin *et al*, 2019	NPC	RT-qPCR of NPC tissue (n=38) and non-cancerous NP tissue (n=23); TMA of NPC tissue (n=177) and non-cancerous NP tissue (n=61)	Univariate analysis: T1-T2 vs. T3-T4: HR, 0.474 (CI, 0.253-0.887), P=0.020; N0-N1 vs. N2-N3: HR, 0.475 (CI, 0.256-0.881), P=0.018; M: No vs. Yes: HR, 0.146 (CI, 0.067-0.318), P<0.001; C: I-II vs. III-IV: HR, 0.481 (CI, 0.255-0.907), P=0.024	Univariate analysis; P<0.05; good prognosis	(56)
Mangé *et al*, 2012	Breast cancer	Microarray of DCIS (n=20) and patients with IBC (n=20); ELISA of DCIS (n=61) and patients with IBC (n=59); IHC of DCIS and IBC specimens (n=20)	AUC in the difference between DCIS and IBC: HR, 0.794 (95% CI, 0.674-0.877)	Log-rank test; P<0.05; good prognosis	(83)
Dankner *et al*, 2021	Breast/lung/other	IHC and TMA, RNA seq of 164 patients with, minimally invasive brain metastasis (n=56) or highly invasive brain metastasis (n=108); breast (n=83); lung (n=38); other (n=43)	IHC H score: MI<HI, P=0.0096	Log-rank test; P<0.05; poor prognosis	(60)

AUC, area under the ROC curve; C, clinical; CI, confidence interval; CIRBP, cold-inducible RNA-binding protein; DCIS, ductal carcinoma *in situ*; GEO, gene expression omnibus; HR, hazard ratio; IBC, invasive breast carcinoma; FDR, false discovery rate; IHC, immunohistochemistry; M, distant metastasis; N, regional lymph nodes; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; PAM, prediction analysis of microarrays; OSCC, oral squamous cell carcinoma; T, primary tumor; TCGA, The Cancer Genome Atlas; TMA, tissue microarray; MI, minimally invasive lesion; HI, highly invasive lesion.

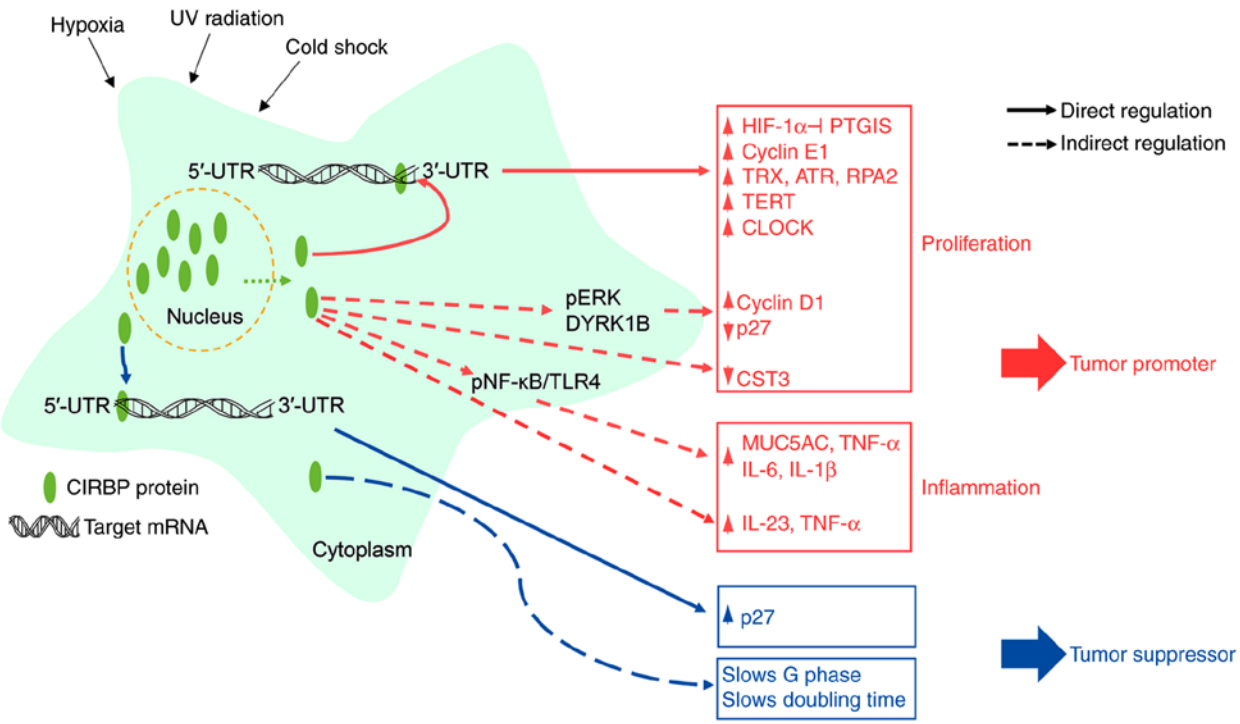

Figure 2. Controversial roles of CIRBP in human cancers. Upon various stresses such as cold shock, UV and hypoxia, CIRBP migrates from the nucleus to the cytoplasm and stabilizes or destabilizes mRNA by binding to the 3'-UTR of target mRNAs encoding HIF-1α, Cyclin E1, TRX, TERT and CLOCK. CIRBP can also increase or decrease the translation of genes, such as cyclin D1, p27, CST3 and inflammatory cytokines by the ERK and NF-κB pathways, and through unidentified mechanisms. CIRBP can act as a tumor promoter by increasing cell growth and decreasing cell apoptosis. Conversely, CIRBP can also function as a tumor suppressor by slowing the G phase and doubling time of cell cycle in different cancer types, or by directly binding to p27 and increasing p27 expression levels. These divergent functions of CIRBP in human cancers indicate that CIRBP can be used as a potential prognostic marker or promising therapeutic target, depending on cancer subtypes. ATR, ATR serine/threonine kinase; CIRBP, cold-inducible RNA-binding protein; CST3, cystatin 3; DYRK1B, dual-specificity tyrosine-phosphorylation-regulated kinase 1B; HIF-1α, hypoxia inducible factor-1α; p, phosphorylated; MUC5AC, mucin-5AC; RPA2, replication protein A2; TERT, telomerase reverse transcriptase; TRX, thioredoxin; UTR, untranslated region; CLOCK, clock circadian regulator.

CIRBP can promote cancer metastasis. Conversely, CIRBP is inversely correlated with lymph node invasion and distant metastasis in nasopharyngeal carcinoma (56). Additionally, CIRBP is differentially upregulated in non-triple negative breast cancer (TNBC) compared with metastasis-related TNBC (63). Although the evidence of CIRBP involvement in metastasis is still incomplete, CIRBP may potentially represent a crucial component of the metastatic process.

To overcome low survival rate of patients with metastatic cancer, it is necessary to identify the biomarkers for early diagnosis before metastasis to distant organs. Recently, genomic profiling analysis using Gene Expression Omnibus and TCGA datasets revealed that high expression levels of CIRBP are correlated with good prognosis in patients with early-stage NSCLC with low metastasis (80). Stratification according to TNM classification revealed that a higher CIRBP expression level is frequently detected in T1-T2, M0 and I-II tumors compared with T3-T4, M1 and III-IV nasopharyngeal carcinoma tissues, respectively (56). Likewise, gene expression profiles based on microarrays have demonstrated that CIRBP is significantly upregulated in benign tumors compared with malignant ovarian cancers (81). Conversely, CIRBP is significantly associated with histological classification, clinical stages and lymph node metastasis in OSCC samples (55). Although it is important to classify the subtypes of breast cancer, there is currently no good parameter to distinguish invasive breast carcinoma (IBC) from ductal carcinoma *in situ* (DCIS) (82). By screening autoantibodies using protein microarrays with DCIS and IBC samples, CIRBP was identified as an autoantibody signature that could discriminate DCIS from IBC. This result indicates that CIRBP may represent a novel prognostic marker in breast cancer (83). CIRBP is also a splicing factor (SF), which are important factors in cancer progression (84,85). By comparing RNA expression levels of various SFs between primary cancer and their metastatic counterparts from TCGA, it was found that CIRBP expression is higher in metastatic tissues compared with original tumors (79). Along with SF, alternative splicing events (ASEs) are also responsible for cancer development and progression (86,87). RNA sequencing and ASE-related datasets of breast cancer samples obtained from TCGA revealed that CIRBP, may serve as a predictor for survival in prognostic-related ASE (59). Together, these results suggest that CIRBP may function as a prognostic marker in a number of cancer types.

5. CIRBP as a therapeutic target for cancer therapy

The use of cytotoxic drugs is the main treatment method for advanced and aggressive cancers, and cancers without specific therapeutic targets. However, resistance to cytotoxic chemotherapy and drug side effects are major barriers to attaining a complete response (88). Several studies have reported that resistance to chemotherapy is enhanced by secretory molecules that can promote the repair signaling coordinated by TLR4 (89,90). CIRBP can trigger the secretion of TNF-α through the

activation of TLR4 and NF-κB in macrophages. Several studies have also reported that CIRBP can mediate inflammatory signaling via regulation of TLR4 signaling (76,91). Based on these results, CIRBP-derived oligopeptides or neutralizing antibodies were demonstrated to ameliorate sepsis-mediated injury of the lung and kidney (15,92,93). These CIRBP antagonists can block the interaction of extracellular CIRBP with TLR4/myeloid differentiation 2 receptor complex to inhibit the downstream signaling (15).

The circadian clock is an important molecular mechanism for the maintenance of homeostasis and its imbalance facilitates tumor progression (94). In various cancer types, circadian genes are associated with chemoresistance and cancer progression (95,96). Thus, there is a novel approach that indirectly or directly targets circadian clock genes to remove cancer and improve survival rates (97,98). Several studies have suggested that CIRBP can be used in cancer treatment by regulating circadian genes (13,68). Chemotherapeutic drugs can induce apoptosis, necrosis and autophagy in cancerous tissues (99,100). As CIRBP exerts a protective role in apoptosis in neurons and cardiac cells, combined therapy of cytotoxic drugs with anti-CIRBP therapeutics may improve the response efficacy and survival rate in patients with neuronal and cardiac abnormalities (101,102).

Small molecules that complement biologics, such as antibodies, have advantages of cost effectiveness and cell permeability for applications in cancer therapy. Several chemical probes targeting specific RBPs have been shown to be able to function as selective inhibitors by modulating RBP-target mRNA interactions (103-107). Recently, it has been reported that a probe can interfere with CIRBP-RNA associations, inhibit cytotoxic T-lymphocyte protein-4 and TRX expression, and suppress the progression of various cancer types without side effects (108). Further studies are needed to apply these CIRBP antagonists for cancer therapy in the future.

6. Conclusions

The present review summarized recent findings about the roles of CIRBP in cancer development, metastasis and cancer therapy (Fig. 2). During cancer proliferation and metastasis, the function of CIRBP appears to be driven primarily by promoting the stability and translation of target mRNAs. Conversely, certain studies have demonstrated that CIRBP serves as a tumor suppressor in cancer progression by modulating the multiple steps of cell proliferation. These controversial roles of CIRBP in human cancers may originate from the alternative splicing of the CIRBP transcript (2,4-6). Differentially expressed splicing variants may interact and modulate the different target mRNAs, depending on cancer subtypes or cell contexts. To understand the exact role of CIRBP in cancers, target mRNAs of each splicing isoform should be identified and the regulatory mechanism analyzed in human cancers. Clinical studies have shown that CIRBP may represent a prognostic marker of cancer progression. Although numerous studies have reported roles of CIRBP in cancer biology, further detailed studies are required to elucidate the exact role of CIRBP in human cancers and to evaluate the potential of the application of CIRBP-targeted cancer therapy.

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Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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