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Review Article

Circular RNA-mediated miRNA sponge & RNA binding protein in biological modulation of breast cancer

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ABSTRACT

Circular RNAs (circRNAs) and small non-coding RNAs of the head-to-junction circle in the construct play critical roles in gene regulation and are significantly associated with breast cancer (BC). Numerous circRNAs are potential cancer biomarkers that may be used for diagnosis and prognosis. Widespread expression of circRNAs is regarded as a feature of gene expression in highly diverged eukaryotes. Recent studies show that circRNAs have two main biological modulation models: sponging and RNA-binding. This review explained the biogenesis of circRNAs and assessed emerging findings on their sponge function and role as RNA-binding proteins (RBPs) to better understand how their interaction alters cellular function in BC. We focused on how sponges significantly affect the phenotype and progression of BC. We described how circRNAs exercise the translation functions in ribosomes. Furthermore, we reviewed recent studies on RBPs, and post-protein modifications influencing BC and provided a perspective on future research directions for treating BC.

1. Introduction

The scientific community has recently become increasingly aware of the crucial roles of non-coding RNAs (ncRNAs) in most malignant cancers. Among them, circular RNAs (circRNAs) (once recognized as a splicing byproduct and now proved as back splicing circRNAs) are promising candidates for additional in-depth research on the regulatory roles in various diseases. CircRNAs were identified in plant viroids in 1976 [1]. A precise isolation method based on RNase R treatment followed by polyadenylation and poly(A) + RNA [2] showed that circRNAs are located at head-to-tail junctions with 30–50 phosphodiester bonds, resulting in an RNA molecule in a circular format [3]. CircRNAs are ncRNAs. They are covalently closed single-stranded RNAs [4] generated by pre-mRNA back-splicing which is a highly stable covalent closed-loop structure conferring huge benefits to regulate specific cell types while preventing exonuclease-mediated degradation [5,6]. The first circular exon in the HeLa cell nuclei was extracted by inverse splicing of the second intron of the human beta-globin gene from a pre-mRNA transcript [7].

The abundance of circRNAs varies among different organs, including the brain, heart, and other organs [8]. Furthermore, the abundance of circRNAs is cell type-specific and correlated with proliferation [9]. CircRNAs exert oncogenic or tumor suppressor functions as miRNA sponges that affect cell proliferation, migration, invasion, apoptosis, and drug resistance. Firstly, T. B. Hansen conducted a functional analysis of a naturally expressed circRNA. CiRS-7 significantly inhibits the activity of miR-7. In the mouse brain, there is considerable co-expression of ciRS-7 and miR-7, especially in neocortical and hippocampal neurons, indicating a substantial level of endogenous interaction [10]. Additionally, circRNA-binding proteins play crucial roles in all aspects of RNA biology, including transcription, modification, stabilization, localization, and translation of small proteins/peptides [11,12]. A census identified approximately 1542 human RNA-binding proteins (RBPs), accounting for 7.5 % of all protein-coding genes [13]. In eukaryotes, transcription and translation processes occur in the nucleus and cytoplasm, respectively. CircFoxo3 [14] displays high binding affinity to transcription factors such as Id-1, E2F1, and HIF-α that results in reduced nuclear translocation [15]. Furthermore, it causes

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mitochondrial translocation of FAK, which promotes cardiac senescence in vitro and in vivo.

Global cancer statistics show that breast cancer (BC) in women is the fifth leading cause of cancer-related morbidity, with a global mortality rate of 6.9 %; 685,000 deaths occurred in 2020 alone. Moreover, female patients with BC account for 11.7 % of the 18.1 million newly reported cancer cases in 2020, exceeding the proportion of patients diagnosed with lung cancer [16]. Breast cancer can be categorized into four molecular subtypes [luminal A (ER/PR+, HER2–,Ki67–), luminal B (ER/PR+, HER2+,Ki67+), HER2-overexpressed (HER2+), and triple-negative breast cancer (TNBC) (ER–, PR–, HER2–)] according to the expression of four biological markers: estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 receptor (HER2), and Ki67 [17].

This review summarizes previous research on how circRNAs regulate BC and their underlying molecular mechanisms. This provides insights into how circular RNAs interact with proteins that may help predict BC in a more effective and precise manner.

2. CircRNAs act as a miRNA sponge to regulate BC

In recent years, there has been a burgeoning body of research focused on the biogenesis and functions of circRNAs. Previous studies have revealed that circRNAs play a crucial role in the regulation of BC, impacting diverse phenotypes including proliferation, metastasis, invasion, epithelial-mesenchymal transition (EMT), apoptosis, and cell cycle progression [18]. Their regulatory mechanism involves functioning as miRNA sponges, thereby contributing to the intricate network of molecular interactions within the context of BC.

2.1. CircRNAs in the regulation of invasion and metastasis in BC

Recent research substantiates circRNAs as promising candidate biomarkers that function as miRNA sponges, exerting influence on mRNA translation and fostering the invasion and metastasis of BC cells through miRNA sequestration. CircRNA directly endogenously compete with miRNA. For example, circ0052112 targets ZNF83 and sponges miR-125a-5p [19] which contributes to promoting BC cell migration and invasion. CircVAPA acts as a sponge to endogenously compete with miR-130a-5p to regulate BC cell migration and invasion [20]. Circular RNAs that act as miRNA sponges highlight the significance of in promoting TNBC.For example, CircEIF3M compete with CCND1 by competing endogenous by binding miR33, which contributes to promote TNBC progression [21]. CircPLK1 sponges miR-296-5p [22], circ0000520 sponges miR-1296 [23], and circ0091074 regulates TAZ expression by sponging mi1297 [24]. Circ0131242 sponges miR2682 [25] and circ0044234 binds GATA3 protein gene and sponges miR-135b-5p [26], which clarifies circRNAs potential in predicting and regulating TNBC.

Certain circRNAs distinctly exhibit the capability to promote cancer metastasis. For example, circIQCH induces the lung cancer metastasis of BC by sponging miR-145 with upregulating DNMT3A expression [27]. CircFBXL5 sponges miR-660 with SRSF6 to promote BC lung progression [28]. Circ0001944 sponges miR-509 and promotes the proliferation of BC cell brain metastasis [29]. CircBCBM1 acts as endogenous miR-125a sponge that results in the upregulation of BRD4 and eventually promotes BC brain metastasis [30]. CircIKBKB promotes BC bone metastasis by sustaining NF-κB/bone remodeling factor signaling [31]. Circ0067934 enhances thyroid cancer metastasis via sponging miR-1304 and regulating CXCR1 expression to exhaust migration and invasion of BC cells [32].

Mechanistically, circRNAs sponge miRNAs and bind to target genes that activate canonical signaling pathways to regulate BC progression (FIG.1.I). For example, circ0005273 sponges miR-200a-3p and regulates the YAP1-hippo signaling pathway [33] in BC patient tissues and cell lines to promote BC progression. CircITCH sponges miR-214 and miR-17 to activate Wnt/β-catenin signaling that promotes TNBC cell proliferation, invasion, and metastasis [34]. CircRNAs act as sponge to miRNAs and most activate non-conical signalling pathways. For example, circCD44 modulates miR-502-5p/KRAS and IGF2BP2/Myc axis [35], circTFCP2L1 sponges miR-7 and inhibits PAK1 expression [36], circUBAP2 modulates the miR-661/MTA1 pathway [37], circPDCD11 sponges miR-432-5p to enhance TNBC lactate dehydrogenase [38], and circRPPH1 promotes TNBC progression through the miR-556-5p/YAP1 axis [39]. These circRNAs play oncogenic roles to promotes the proliferation and migration of TNBC and predict a poor prognosis of TNBC.

CircRNAs suppress BC progression by sponging miRNAs. CircNFIC suppresses BC progression by sponging miR-658 [40], while circTADA2A-E6 sponges miR-203a-3p and suppresses BC progression and cell metastasis [41]. However, TNBC is regulated by circRNA-miRNA-translation factors. CircAHNAK1 sponges miR-421 to regulate RASA1 which inhibits proliferation and metastasis of TNBC cells [42]. CircCDYL acts as a tumor suppressor of TNBC by sponging miR-190a-3p and upregulating TP53INP1 expression [43]. CircFBXW7 inhibits the malignant progression of TNBC by sponging miR-197-3p and encoding a 185-aa protein [44]. CircNR3C2 promotes HRD1-mediated tumor suppressive effects by sponging miR513a-3p in TNBC [45].

In addition, circRNAs suppress BC and activate signaling pathways in canonical and non-canonical pathways by sponging miRNAs. CircKDM4B sponges miR-675 and targets NEDD4 to regulate the typical PI3/ART signaling pathway [46]. CircNOL10 suppresses BC cell proliferation and migration by sponging miR-767-5p to regulate the SOCS2/JAK/STAT pathway [47]. Circ000911 inhibits BC cell viability, migration, and invasion by sponging miR449a and activating the Notch1 signaling pathway [48]. CircEHMT1 inhibits the metastatic potential of BC cells by modulating the miR-1233-3p/KLF4/MMP2 axis [49] (Fig. 1 I).

2.2. CircRNAs regulate BC cell proliferation

Proliferation is the process by which cells grow due to the division of progenitor cells before full differentiation [50]. Circular RNAs have potential as biomarker candidates to regulate BC proliferation by sponging miRNAs. For instance, circABCB10 promotes BC cell proliferation by sponging miR-1271 [51], circACAP2 directly sponges miR-29a/b-3p and modulates COL5A1 [52], circOMA1 sponges miR-1276 and binds to SIRT4 [53], circPTCD3 sponges miR-198 [54], circPRMT5 is upregulated in BC cells and promotes BC cell proliferation [55]. These processes directly target genes that induce BC cell proliferation.

CircRNAs promote BC cell proliferation and invasion, and occasionally activate the signaling axis which provides a perspective for BC future research direction. CirCHIPK3 promotes BC cell proliferation and invasion by sponging miR-193a, thereby affecting the HMGB1/PI3K/AKT axis [56].Circ0001667 sponges miR-125a-5p and modulates TAZ, which activates the Hippo pathway [57] and promotes BC cell proliferation. CircEIF6 promotes TNBC cell proliferation and metastasis by stabilizing MYH9, which activates the Wnt/beta-catenin pathway [58]. miR-186-5p and miR-548c-3p mediate the modulatory effect of circBACH2 in promoting the proliferation of TNBC cells that promotes EMT progression and BC cell proliferation [59].CircPGAP3 promotes proliferation and invasion by regulating the miR-330-3p/myc axis [60]. Circ069718 promotes TNBC cell proliferation and invasion by activating the Wnt/β-catenin pathway [61]. Circ0001944 sponges miR-509 and promotes the proliferation of BC cell brain metastasis [29]. In contrast, circ _0001785 inhibits BC cell proliferation by sponging miR942 [62].

CircRNA can induce competing endogenous RNAs (ceRNAs) to act as sponges. Furthermore, circRNAs interact with mRNAs by upregulating or downregulating the expression of specific genes in BC tissues and cell lines to potentially promote or suppress BC cell proliferation, migration, and invasion (Tables 1 and 2).

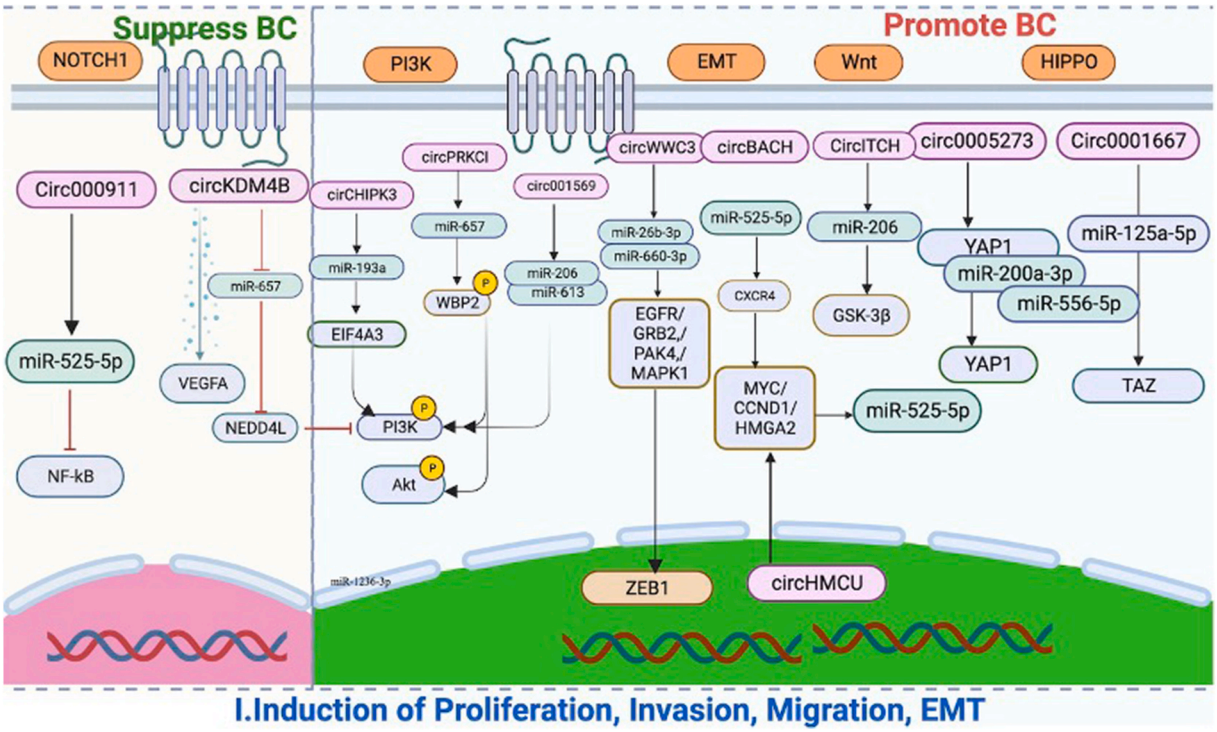

Fig. 1. ***I*:**CircRNAs contribute to regulate BC and induce kinds of phenotypes including proliferation, metasatasis, invasion,EMT, apoptosis and cell cycle. Canonical signaling pathways as NOTCH1, PI3K/Akt, Wnt, Hippo and EMT were activated by circRNAs. CircRNAs were investigated to act as sponges and compete endogenous with miRNAs to regulate BC progression.

Table 1
CircRNAs sponge miRNA to promote BC.

CircRNA	Gene	Sponge	Pathway/Axis	Phenotypes	Reference
Circ_0000442	PTEN	miR-148b-3p	PI3K/Akt	proliferation	[138]
Circ_0001666	WNK2	miR-620	miR-620/WNK2	proliferation, migration, invasion, and apoptosis	[139]
Circ_0001667	TAZ	miR-125a-5p	Hippo	inhibition proliferation and metastasis	[140]
Circ_0001785	Socs3	miR-942	miR-942/SOCS3	proliferation, migration, and invasion	[141]
Circ_000554	ZFP36	miR-182	miR-182/ZFP36	migration, EMT	[142]
Circ_000911	NF-κB	miR-449a	Notch1	cell viability, migration, and invasion	[143]
Circ_0025202	FOXO3a	miR-182-5p	miR-182-5p/FOXO3a	proliferation, migration, apoptosis, and tamoxifen drug resistant	[144]
Circ_0043278	EI24	miR-455-3p	circ0043278/miR-455-3p/EI24	migration and invasion	[145]
Circ_0047604	DACH1	miR-548o	circ0047604/miR-548o/DACH1	proliferation, migration	[146]
Circ_0053063	PDCD4	miR-330	miR-330-3p/PDCD4	proliferation	[147]
Circ_0068033	Bcl-2	miR-659	circ_0068033/miR-659	proliferation, invasion, migration, and apoptosis	[148]
Circ_0102273	PFKFB3	miR-1236-3p	miR-1236-3p/PFKFB3	proliferation, metastasis, and glycolysis	[149]
Circ_CDYL	TP53INP1	miR-190a-3p	miR-190a-3p/TP53INP1	proliferation, colony formation, cell migration, and invasion	[150]
Circ_EHMT1	KLF4	miR-1233-3p	miR-1233-3p/KLF4/MMP2	migration, invasion, and metastasis	[151]
Circ_KDM4B	NEDD4	miR-675	PI3K/AKT	migration and invasion	[152]
Circ_KDM4C	PBLD	miR-548p	miR-548p/PBLD	proliferation, and doxorubicin resistant	[153]
Circ_RPPH1	HMGA2	miR-328-3p	miR-328-3p/HMGA2	proliferation, glycolysis	[154]
Circ_SETD2	SCUBE2	miR-155-5p	miR-155-5p/SCUBE2	proliferation, migration, invasion, cell cycle, and apoptosis	[155]
Circ_TADA2As	SOCS3	miR-203a-3p	miR-203a-3p/SOCS3	proliferation, migration, and EMT	[156]

2.3. CircRNAs in the regulation of the epithelial-mesenchymal transition (EMT) of BC

Epithelial-mesenchymal transition is a process whereby epithelial cells lose their epithelial characteristics and acquire mesenchymal features that induce cancer progression toward malignant cell migration, invasion, and metastasis [63]. Loss or gain of ZEB-1, Snail, or Slug expression can be used to define EMT. CircRNAs activate EMT and significantly promote BC cell migration, invasion, and metastasis. CircHMCU sponges let-7 family members and modifies the EMT pathway to promote the migration and invasion of BC [64]. ZEB1 is transcription factor that upregulates circWWC3 to promote BC cell proliferation, migration, and invasion by activating the Ras signaling pathway by sponging miR-26b-3p and miR660-3p [65]. CircKIF4A regulated ZEB1 expression by targeting miR-152 in BC cells which promote BC cell migration and invasion and inhibit apoptosis [66]. The EMT enhances cell stemness to promote cell migration. Circ002178 promotes BC cell migration and maintains cancer stem-like cell properties by regulating the miR-1258/KDM7A axis [67]. CircSCYL2 causes EMT in BC cells and significantly correlates with poor patient prognosis [68]. CXCL13-CXCR5 co-expression regulates EMT in BC cells during lymph node metastasis [69]. Circ001569 is an unfavorable prognostic factor that promotes cell proliferation and metastasis by modulating the PI3K-AKT pathway in BC, inducing apoptosis of BC cells, and influencing EMT marker expression [70] (Fig. 1. I).

Table 2
CircRNAs sponge miRNA to suppress BC.

CircRNA	Gene	Sponge	Pathway/Axis	Phenotypes	Reference
Circ_0000043	Smad3	miR-136	miR-136/Smad3	proliferation, migration, invasion, and EMT	[157]
Circ_0000291	ETS1	miR-326	miR-326/ETS1	proliferation, migration, invasion, and EMT	[158]
Circ_0000442	PTEN	miR-148b-3p	PI3K/Akt	cell cycle, proliferation	[159]
Circ_0000511	TAZ	miR-326	miR-326/TAZ	proliferation, migration and invasion, and apoptosis	[160]
Circ_0000515	CXCL10	miR-296-5p	miR-296-5p/CXCL10	proliferation, migration, and invasion	[161]
Circ_0000515	CXCL10	miR-296-5p	miR-296-5p/CXCL10	proliferation, invasion, angiogenesis, and inflammatory response	[161]
Circ_0000520	SP1	miR-1296	miR-1296/SP1	proliferation, migration, invasion, and apoptosis	[162]
Circ_0003645	HMGB1	miR-139-3p	miR-139-3p/HMGB1	proliferation and apoptosis	[163]
Circ_0004771	ZEB2	miR-653	circ_0004771/miR-653/ZEB2	proliferation and apoptosis	[164]
Circ_0005230	CBX8	miR-618	circ_0005230/miR-618/CBX8	proliferation, apoptosis, metastasis, and invasion	[165]
Circ_0005273	YAP1	miR-200a-3p	Hippo	proliferation, migration, and cell cycle	[166]
Circ_0006528	CDK8	miR-1299	miR-1299/CDK8	proliferation, migration, invasion and autophagy, and apoptosis	[167]
Circ_0006528	CHD4	miR-1236-3p	miR-1236-3p/CHD4	proliferation, migration, invasion, and ADM drug resistance	[168]
Circ_0006528	Raf1	miR-7-5p	MAPK/ERK	proliferation, invasion, cell cycle and migration	[169]
Circ_0007255	SIX2	miR-335-5p	miR-335-5p/SIX2	migration, invasion, and metastasis	[170]
Circ_0008039	E2F3	miR-432-5p	miR-432-5p/E2F3	proliferation and migration	[171]
Circ_0008039	CBX4	MiR-515-5p	miR-515-5p/CBX4	proliferation, migration, and invasion	[172]
Circ_0008039	SKA2	miR-140-3p	miR-140-3p/SKA2	promote proliferation, migration, invasion, and glycolysis	[173]
Circ_0008500	PFN2	miR-758-3p	miR-758-3p/PFN2	proliferation, apoptosis	[174]
Circ_0008673	CFL2	miR-153-3p	miR-153-3p/CFL2	proliferation, migration and invasion, and repressed cell apoptosis	[175]
Circ_002178	KDM7A	miR-1258	miR-1258/KDM7A	proliferation and migration	[176]
Circ_0048764	TRIM14	miR-1296-5p	miR-1296-5p/TRIM14	proliferation, migration, and invasion and inhibits apoptosis	[177]
Circ_0061825	FGFR3	miR-593-3p	miR-593-3p/FGFR3	proliferation, migration, invasion, cell cycle and apoptosis	[178]
Circ_0069094	HK2	miR-591	miR-591/HK2	apoptosis, inhibit proliferation, and reduced glycolysis	[179]
Circ_0072995	SHMT2	miR-149-5p	miR-149-5p/SHMT2	migration and glycolysis	[180]
Circ_0084927	ERC1	miR-142-3p	miR-142-3p/ERC1	proliferation, colony formation, and invasion	[181]
Circ_0085495	integrin β1	miR-873-5p	miR-873-5p/integrin β1	proliferation, metastasis, and Adriamycin drug resistance	[182]
Circ_0089153	E2F6	miR-2467-3p	miR-2467-3p/E2F6	proliferation, migration, invasion and EMT	[183]
Circ_0089153	SENP1	miR-198	miR-198/SENP1	proliferation and metastasis	[184]
Circ_0102273	PFKFB3	miR-1236-3p	miR-1236-3p/PFKFB3	proliferation, metastasis, and glycolysis	[185]
Circ_ABCB10	DUSP7	Let-7a-5p	Let-7a-5p/DUSP7	apoptosis, invasion, autophagy and PTX drug resistant	[186]
Circ_ABCB10	PFN2	miR-223-3p	miR-223-3p/PFN2	proliferation, glycolysis, colony formation, and drug resistance	[187]
Circ_ACAP2	COL5A1	miR-29a/b-3p	miR-29a/b-3p/COL5A1	proliferation and viability	[188]
Circ_ARL8B	HMGA2	miR-653-5p	miR-653-5p/HMGA2	viability, migration, invasion, and fatty acid metabolism	[189]
Circ_BACH2	HNRNPC	miR-944	MAPK	proliferation	[190]
Circ_BARD1	BARD1	miR-3942	miR-3942/BARD1	proliferation, block cell cycle and promote cell apoptosis	[191]
Circ_BCBM1	BRD4	miR-125a	circBCBM1/miR-125a/BRD4	proliferation and migration, and brain metastasis	[192]
Circ_BMPR2	USP4	miR-553	circBMPR2/miR-553/USP4	proliferation, Migration, Invasion and TAM Resistance	[193]
Circ_CDYL	ATG7/ULK1	miR-1275	miR-1275/ATG7/ULK1	proliferation and autophagy	[194]
Circ_CNOT2	BHLH	miR-409-3p	EMT	promote invasion, migration and EMT	[195]
Circ_DCAF6	GLI1	miR-616-3p	Hedgehog	proliferation and stemness	[196]
Circ_EIF3M	Cyclin D1	miR-33a	circEIF3M/miR-33a/CCD1	proliferation, migration	[197]
Circ_ERBB2	TFAP2C	miR-198	circ-ERBB2/miR-198/TFAP2C	proliferation, migration, invasion, and apoptosis	[198]
Circ_FAT1	SKA1	miR-525-5p	Notch and Wnt	OX-resistant, apoptosis and repress metastatic	[199]
Circ_FBXL5	SRSF6	miR-660	circFBXL5/miR-660/SRSF6	proliferation and migration	[200]
Circ_FBXL5	HMGA2	miR-216b	miR-216b/HMGA2	migration, invasion, apoptosis and 5-fluorouracil drug resistance	[201]
Circ_FOXK2	IGF2BP3	miR-370	IGF2BP3/miR-370	metastasis	[202]
Circ_GFRA1	AIFM2	miR-1228	circGFRA1-miR-1228-AIFM2	proliferation, migration, and invasion	[203]
Circ_HIPK3	HK2	miR-1286	miR-1286/HK2	paclitaxel resistance, cell colony, cell cycle, and apoptosis	[204]
Circ_HIPK3	HMGB1	miR-193a	miR-193a/HMGB1/PI3K/AKT	proliferation and invasion	[205]
Circ_HMCU	HMGA2, CCND1	let-7	EMT	cell cycle, proliferation, and apoptosis	[206]
Circ_IQCH	DNMT3A	miR-145	circIQCH/miR-145/DNMT3A	proliferation and metastasis	[207]
Circ_IRAK3	FOXC1	miR-3607	circIRAK3/miR-3607/FOXC1	proliferation, migration, invasion, and apoptosis	[208]
Circ_KIF4A	ZEB1	miR-152	miR-152/ZEB1	migration, invasion, and apoptosis	[209]
Circ_METTL3	CDK1	miR-31-5p	circMETTL3/miR-31-5p/CDK1	proliferation, migration, and invasion	[210]
Circ_NFIC	UPK1A	miR-658	circNFIC/miR-658/UPK1A	proliferation and migration	[211]
Circ_NINL	ADAM9	miR-921	β-catenin	proliferation, migration, and apoptosis	[212]
Circ_OMA1	SIRT4	miR-1276	miR-1276/SIRT4	proliferation, migration, invasion, and apoptosis	[213]
Circ_PLK1	IGF1	miR-4500	circPLK1/miR-4500/IGF	proliferation, migration, and invasion	[214]
Circ_PRMT5	TCF7L2	miR-509-3p	PI3K/AKT	proliferation, apoptosis, and angiogenesis	[215]
Circ_RASSF2	HOXA1	miR-1205	miR-1205/HOXA1	proliferation, clone formation ability, migration, and invasion	[216]
Circ_RHOT1	STAT3	miR-106a-5p	mir-106a-5p/STAT3	promotes progression and inhibits ferroptosis	[217]
Circ_RNF20	HIF-1α/HK2	miR-487a	miR-487a/HIF-1α/HK2	proliferation, glycolysis	[218]
Circ_RPPH1	ARHGAP1	miR-542-3p	EMT	migration, invasion, apoptosis, and EMT	[219]
Circ_RPPH1	E2F2	miR-146b-3p	circ_RPPH1/miR-146b-3p/E2F2	proliferation, migration, and metastasis	[220]
Circ_RPPH1	FOXP4	miR-296-5p	miR-296-5p/FOXP4	migration, invasion, and glycolysis	[221]
Circ_RPPH1	STAT1	miR-512-5p	circRPPH1-miR-512-5p-STAT1	proliferation, migration, metastasis, and colony formation	[222]
Circ_SEPT9	SLC1A5	miR-149-5p	circSEPT9/miR-149-5p/SLC1A5	proliferation and apoptosis	[223]
Circ_TFF1	FGFR1	miR-338-3p	miR-338-3p/FGFR1	proliferation, apoptosis, invasion, and glycolysis	[224]
Circ_TFF1	TFF1	miR-326	miR-326/TFF1	proliferation, migration, invasion, apoptosis and EMT	[225]
Circ_TP63	FOXM1	miR-873-3p	miR-873-3p/FOXM1	proliferation, cell cycle, invasion, and migration	[226]
Circ_TPGS2	TRAF6	miR-7	circ-TPGS2/miR-7/TRAF6/NF-κB	migration and EMT	[227]
Circ_UBE2D2	CDCA3	miR-512-3p	miR-512-3p/CDCA3	cell viability, metastasis, and tamoxifen drug resistance	[228]

(*continued on next page*)

Table 2 (*continued*)

CircRNA	Gene	Sponge	Pathway/Axis	Phenotypes	Reference
Circ_UBR1	CCND1	miR-1299	miR-1299/CCND1	proliferation, metastasis, and apoptosis	[229]
Circ_WAC	E2F3	miR-599	miR-599/E2F3	proliferation, migration, invasion, apoptosis, and glycolysis	[230]
Circ_WHSC1	FASN	miR-195-5p	AMPK	proliferation, migration, and invasion	[231]
Circ_WWC3	ZEB1	miR-26b-3p, miR-660-3p	Ras	proliferation, migration, and invasion, and EMT	[232]
Circ_ZFR	FABP7	miR-223-3p	Circ_ZFR/miR-223-3p/FABP7	promote proliferation, migration, invasion, apoptosis and EMT	[233]
Circ_ZFR	HIF1A	miR-578	miR-578/HIF1A	proliferation, migration, invasion, glycolysis, and cell apoptosis	[234]
Circ_ZNF609	p70S6K1	miR-145-5p	miR-145-5p/p70S6K1	proliferation, migration, and invasion	[235]

2.4. CircRNAs in the regulation of BC cell apoptosis and the cell cycle

CircRNAs induce cell apoptosis and proptosis and regulate the cell cycle in BC.

Apoptosis is a cell death process activated by inflammasome sensors and culminates in the loss of plasma membrane integrity. It is triggered by the intrinsic pathway is related to B-cell lymphoma-2 (BCL-2) family proteins, particularly through BAK and BAX oligomerization that form pores in the mitochondrial outer membrane [71]. Circ0068033 suppresses the progression of BC by sponging miR659 and disturbing the expression of Bcl-2 protein, which promotes apoptosis of BC cells [72]. CircPVT1 facilitates BC cell apoptosis by regulating miR-29a-39 expression [73]. CircERBB2 promotes HER2-positive BC progression and cell metastasis by sponging miR-136-5p and miR-198 and accelerating cell apoptosis [74]. Circ102229 regulates the miR-152-3p/PFTK1 pathway, which enhances TNBC progression [75] (Fig. 3III).

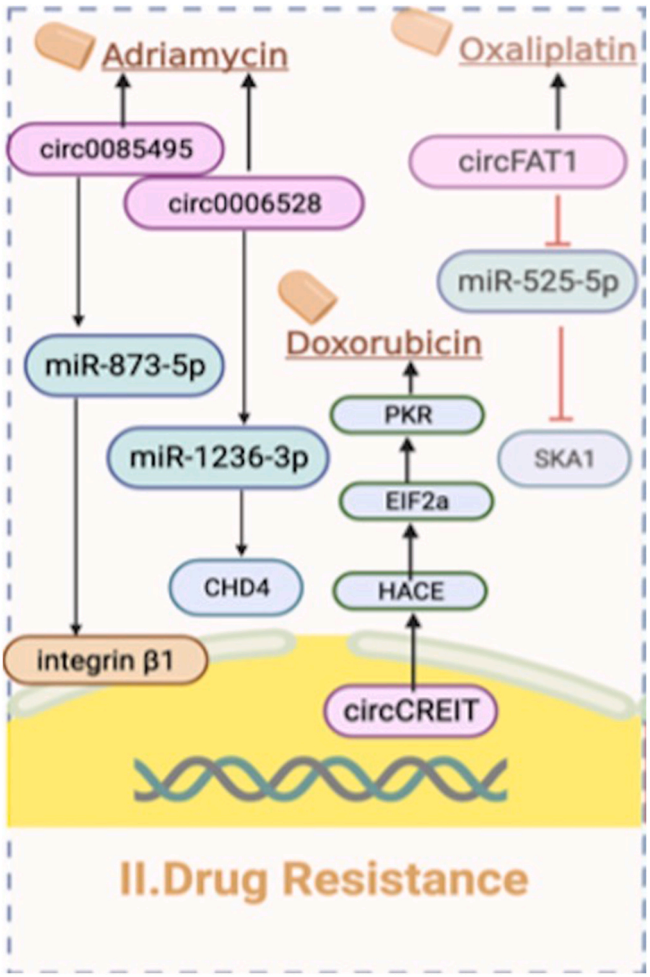

Fig. 2. ***II:***CircRNAs promote chemotherapies drug resistance, for axample, ADM,OX,DOX.

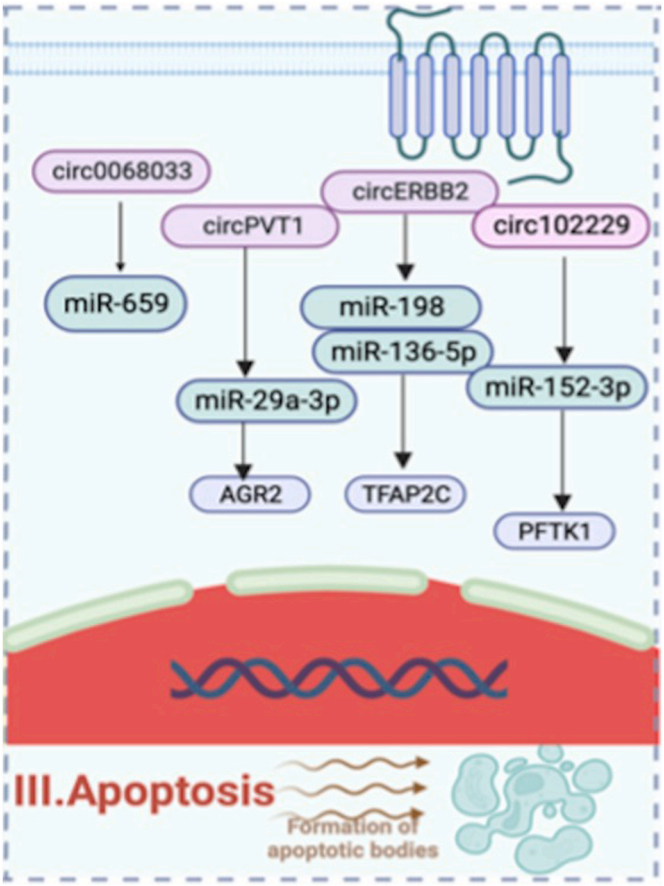

Fig. 3. *III:* Apoptosis is a cell death process activated by inflammasome sensors and culminates in the loss of plasma membrane integrity. CircRNAs induce cell apoptosis of BC.

The accurate transition from the G1 phase of the cell cycle to the S phase is crucial for controlling eukaryotic cell proliferation, and its misregulation promotes oncogenesis [76]. CircIFI30 knockdown leads to cell cycle arrest at the G1 phase in TNBC cells [77]. These results suggest that circACTN4 silencing causes G1 arrest in BC cells [78]. CircPSMA1 facilitates metastasis and cell migration in TNBC through the miR-637/Akt1/β-catenin (cyclin D1) axis and regulates cell cycle arrest in G1 and apoptosis [79]. CircSEPT9 expression is mediated by E2F1 and EIF4A3 to facilitate cell cycle arrest in the G1 phase in TNBC [80]. CircAGFG1 promotes cell cycle modulation, resulting in G1 arrest of TNBC cells [81] (Fig. 4IV).

2.5. CircRNAs in the regulation of drug resistance in BC

Mammography (a serum tumor marker examination) and tissue biopsy are existing strategies for the early diagnosis of BC. Patients with operable BC are administered adjuvant therapy after surgery or neoadjuvant therapy before surgery [82]. The selection of these drugs is

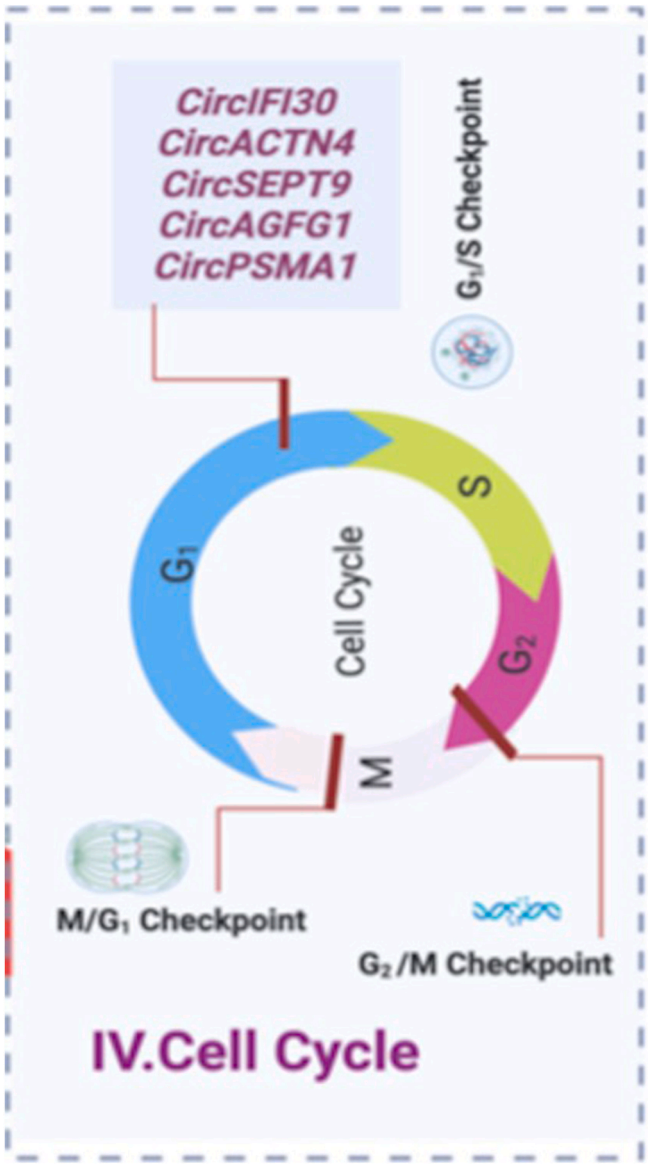

Fig. 4. *IV:* CircRNAs regulate cell cycle in BC, however, mainly in G1/S stage.

determined by the baseline risk estimated by lymph node metastases and invasiveness of the tumor [83]. Premenopausal patients with ER-positive BC are administered tamoxifen as hormone therapy [84]; however, it may induce an increased risk of endometrial cancer as an adverse event specific to patients aged 54 years and above [85]. Trastuzumab is regarded as an anti-HER2 molecular target therapy drug [86].

This review summarizes previous research on how circRNAs regulate BC and their underlying molecular mechanisms. This provides insights into how circular RNAs interact with proteins that may help predict BC in a more effective and precise manner. Common chemotherapies in BC therapeutics include anthracycline, doxorubicin (DOX), alkylating agent cyclophosamide, antimicrotubule agent taxane, and antimetabolite fluorouracil (5-FU); however, circRNAs induce drug resistance. Circ0085495 takes up miR-873-5p and positively regulates integrin β1 expression to suppress and impact adriamycin (ADM) resistance in BC [87]. CircRNF111 promotes PTX BC cell viability, colony formation, invasion, and glycolysis by modulating miR140-5p expression [88]. CircCDYL2 promotes trastuzumab resistance by sustaining HER2 downstream signaling in BC and inhibiting the proteolytic ubiquitination of GRB7 [89]. Circ0025202 regulates tamoxifen sensitivity by regulating the miR-182-5p/FOXO3a axis in BC [90]. CircFBXL5 promotes 5-FU resistance in BC [91] cells. The circFAT1/microRNA-525-5p/spindle and kinetochore-associated complex subunit 1 (SKA1) axis regulate the Notch and Wnt signaling pathways along with OX resistance [92].

Triple-negative breast cancer accounts for 10–15 % of all BC cases and is recognized as the most heterogeneous of all BC types. Besides, some circRNAs show drug resistance to conventional chemotherapies, especially in TNBC [93]. Circ0000199 facilitates the tolerance of cisplatin, adriamycin, paclitaxel, and gemcitabine in TNBC [94]. Circ0006528 promotes the proliferation of BC cells by inducing cell cycle arrest, consequently activating the MAPK/ERK signaling pathway and inducing PTX drug resistance [95]. Furthermore, circ0006528 results in ADM drug-resistance that promotes cell proliferation, migration, and invasion through the miR-1236-3p/CHD4 axis [96]. Doxorubicin is a first-line chemotherapeutic agent used for TNBC treatment. CircCREIT inhibits stress granule assembly and overcomes DOX resistance in TNBC by destabilizing double-stranded RNA-activated protein kinase PKR through the PKR/eIF2α axis [97]. CircUBE2D2 promotes cell proliferation, metastasis, and chemoresistance in TNBC by sponging miR-512-3p [98]. CircGFRA1 functions as a sponge for miR-361-5p and affects the sensitivity of TNBC cells to PTX through the miR-361-5p/TLR4 pathway [99] (Fig. 2II).

2.6. CircRNAs in the regulation of glycolysis in BC

Increased glucose uptake and aerobic glycolysis are the two primary biochemical characteristics of glucose metabolism in cancer cells [100]. Glycolysis produces ATP at a faster rate than oxidative phosphorylation and favors the growth of cancer cells by increasing the levels of lipids, nucleotides, NADPH, and amino acids [101]. A high level of aerobic glycolysis is a hallmark of cancer by detecting the HK2 level. CircRNF20 glycolysis promotes tumorigenesis of BC through the miR-487-a/HIF-1α/HK2 axis [102]. Circ0072995 promotes BC cell carcinogenesis and anaerobic glycolysis by sponging miR-149-5p [103]. CircDENND4C knockdown inhibits glycolysis by upregulating miR-200b/c in BC under hypoxia [104].Interestingly, some circRNAs elevate the aerobic glycolysis levels to facilitate TNBC growth. For example, circERBB2 increases glycolysis and facilitates TNBC cell growth by modulating the 136-5p/pyruvate dehydrogenase kinase 4 axis [105]; circIQCH sponges miR-145 to promote BC progression by upregulating DNMT3A expression [27]; circGNB1 sponges miR-141-5P and promotes TNBC cell proliferation through the circGNB1-miR-141-5p-IGF1R axis [106]; circ0008039 promotes BC cell proliferation, migration, invasion, and glycolysis by regulating the miR-140-3p/SKA2 axis [107]; circ _0102273 promotes BC cell proliferation, metastasis, and glycolysis by sponging miR-1236-3p [108].

2.7. CircRNAs in the regulation of proangiogenic cytokines in BC

Recently, the importance of immune responses in cancer studies was identified, and there is no doubt that the immune system plays a key role in cancer recognition and eradication. Cytokines, chemokines, and growth factors are small molecules secreted by stromal, immune, and/or tumor cells to coordinate and fine tune the immune response [109]. Circ0076611 regulates the translation rate in TNBC and affects the expression of proangiogenic cytokines VEGFA [110]. Circ0000515 is implicated in the development of BC through the regulation of the microRNA-296-5p/CXCL10 axis and facilitates angiogenesis and inflammatory responses [111].

3. CircRNAs modulate RBPs and induce post-translational modifications (PTMs)

RNA binding proteins interact with circRNAs, which are involved in many aspects of the circRNAs cicular life cycle as post-transcriptional

regulation, translation, and specific modifications. The following part summarized how circRNAs result in modification by binding protein.

Post-translational modifications are covalent processing events that occur in eukaryotes and change the protein's properties through proteolytic cleavage or the addition of a modifying group to one or more amino acids. Proteins PTMs are not "decorations" [112]; for example, in signaling, kinase cascades are turned on and off by the reversible addition and removal of phosphate groups [113].

3.1. Methylation

Several studies report modifications in eukaryotic mRNAs, including N1-methyladenosine (m^1A), N6-methyladenosine (m^6A), and 5-methylcytosine (m^5C). m^6A induces methylation activities and comprises two individual proteins: methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and Wilms' tumor 1-associating protein (WTAP) [12,114]. m^6A promotes circRNA biogenesis and translation in human cells.

More recently, m^6A-modified circRNAs enhance the function of circNSUN2 in the cytoplasm [115] that enhance the stability of AT-hook protein 2 mRNA in the high-mobility group. This promotes colorectal cancer cell metastasis. Two m^6A RNA methylation regulators with prognostic value identified in patients with BC (HNRNPC and YTHDF3) correlate with late clinical stages and short survival times along with the MAPK signaling pathway in BC [116]. CircMETTL3 acts as a sponge of miR-34c-3p and inhibits cell proliferation, invasion, tumor growth, and metastasis by upregulating expression of the miR-34c-3p target gene, METTL3 [117].

3.2. Ubiquitination

Ubiquitin involves the covalent attachment of the 76-amino acid protein ubiquitin onto protein substrates [118]. This is a central regulator of all molecular steps of autophagy flux, from the nucleation of the double membrane to the shutdown of the entire process after resolution of the stress situation. E1 catalyzes the formation of a covalent thioester bond between the catalytic cysteine and the di-glycine motif on the C-terminus of ubiquitin by a magnesium ion and ATP and is delivered to E2. E3 binds to E2 ubiquitin and facilitates binding to the target protein [119]. E3 is responsible for diverse ubiquitination patterns in a cell among the three enzymes, and the biological functions related to ubiquitin and ubiquitin-like proteins are not fully elucidated [118].

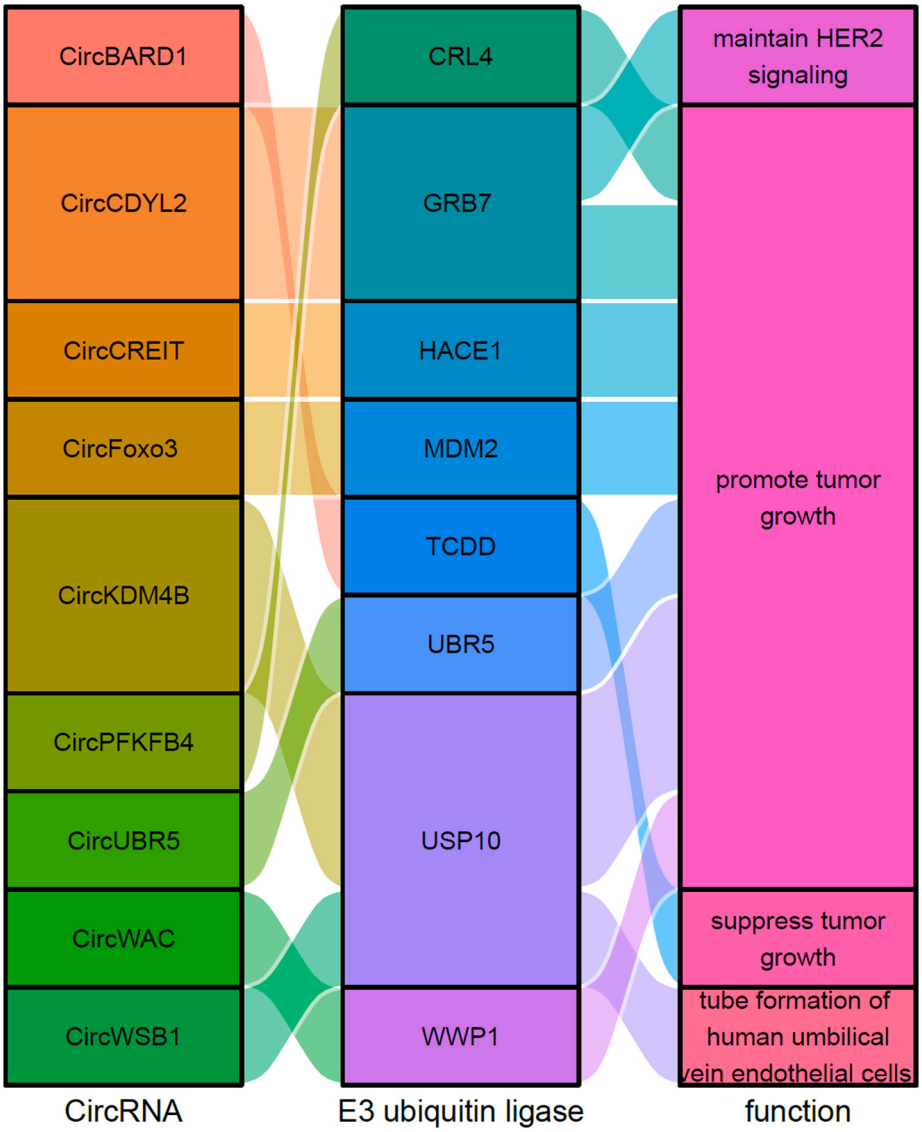

Fig. 5. Sankey diagram of circRNAs, E3 ubiquitin ligase and function in BC. USP10 is one of the key E3 ubiquitin ligase which be found a proliferation promotor enzyme for BC and an induction of tube formation of human umbilical vein endothelial cells.

Mechanistically, circKDM4B catalyzes PI3KCA ubiquitination to upregulate the expression of NEDD4-like E3 ubiquitin-protein ligase, thereby inhibiting PI3K/AKT and VEGFA secretion [46]. CircWSB1 directly binds to USP10 to stabilize and deubiquitinate p53, thereby inhibiting BC cell proliferation [120]. The circ-Foxo3-p53-MDM2 interaction may add a layer of action for MDM2 to interact with mutant p53, leading to the ubiquitination of mutant p53 [14]. CircPFKFB4 promotes the ubiquitination and degradation of p27 by mediating E3 ubiquitin ligase under hypoxia [121]. CircCDYL2 inhibits the proteolytic ubiquitination of GRB7 [89]. CircUBR5 is derived from exons 2, 3, 4, and 5 of the E3 ubiquitin ligase UBR5, and the circUBR5/miR-1179/UBR5 axis may facilitate TNBC [122]. HIF1α binds to hypoxia response elements in the promoter region of the PFKFB4 gene to facilitate the biogenesis of circPFKFB4 under hypoxia. Hypoxia-induced circPFKFB4 directly binds to DDB1 and DDB2 and promotes the assembly of CRL4 (DDB2) E3 ubiquitin ligase, resulting in p27 ubiquitination and BC progression under hypoxia [121]. CircCREIT acts as a scaffold to facilitate the interaction between PKR and the E3 ligase HACE1 and promotes proteasomal degradation of the PKR protein through K48-linked polyubiquitination [97]. CircWAC [123] activates the PI3K/AKT signaling pathway, and its expression is negatively correlated with miR-142; this inhibits the expression of WW domain-containing E3 ubiquitin protein ligase 1 (Fig. 5).

3.3. Phosphorylation

Phosphorylation plays an important role in cell growth, differentiation, apoptosis, and signaling under healthy conditions. Tyrosine kinase, MAP kinase, cadherin-catenin complex, and cyclin-dependent kinase are major players in the cell cycle and deregulation of phosphorylation-dephosphorylation cascade [124]. 12(S)-HETE elevates Ca^{2+} levels in LEC by activating PLC/IP3. Ca^{2+}-calmodulin kinase MYLK contributes to Ser19-MLC2 phosphorylation, LEC contraction, and CCID formation. The spread of BC through the lymphatic system may be reduced under this mechanism (in association with lidoflazine, ketotifen, epiandrosterone, and cyclosporine) [125]. Circ-TPGS2 acts as a sponge of miR-7 and elevates TRAF6 expression, leading to p65 phosphorylation and nuclear translocation, and ultimately activating the NF-κB signaling pathway to facilitate BC metastasis [126]. CircSEMA4B negatively regulates the PI3K/AKT signaling pathway and inhibits AKT (Ser473) phosphorylation through the miR-330-3p/PDCD4 axis. SEMA4B-211aa inhibits PIP3 generation by binding to p85, thereby inhibiting AKT (Thr308) phosphorylation [127].

4. Translation

Most studies demonstrate that circRNAs are non-coding and primarily function by sponging miRNAs and sequestering and regulating RBPs. However, recent evidence suggests that some circRNAs may function through the proteins they encode, although specific mechanisms and examples require further elucidation.

In contrast to linear mRNAs, which rely on the eukaryotic initiation factor 4F complex (eIF4) to anchor the 5′ cap for translation initiation, circRNAs lack the 5′ cap and polyA tails at the 3′ ends. Consequently, the translation of circRNAs is cap independent. Notably, oligo-split-eGFP circRNA reporter screens have been employed to detect the presence of an internal ribosome entry site (IRES), facilitating cap-independent translation. These screens contribute to our understanding of the unique translation mechanisms employed by circRNAs [128,129].

EIF4A3 was found to bind to circZFAND6 pre-mRNA transcript upstream region, leading to the high expression of circZFAND6 in BC [130]. Mecaniclly, circMYBL2 upregulated the transcription factor E2F1 by sponging miR-1205 and complexing with EIF4A3 in BC cells [131]. EIF4A3 is a translation initiation factor that can bind to circPRKCI, which regulates WBP2 and AKT phosphorylation to promote TNBC progression [132]. Circ0068631 promotes BC progression by facilitating c-Myc and binds to EIF4A3 [133]. EIF4A3-mediates circ0088088 expression to promote BC cell proliferation and metastasis by sponging miR-135-5p [134].

5. Conclusions and perspective

Most circRNAs are present in the cytoplasm [135]. Their unique structures, devoid of 5′ end caps or 3′ poly(A) tails, render them exceptionally stable and resistant to degradation by most RNA decay machinery. Furthermore, the miRNA target sites of circRNA sponges exhibit minimal polymorphisms, ensuring the conservation of circRNAs and making them a popular focus for investigation. They play critical roles in various cancers, including glioma, esophageal squamous cell carcinoma, and thyroid cancer.

Most circRNAs are untranslated; however, several recent studies confirmed that certain circRNAs can be initiated by a cap-independent mechanism that requires an IRES [136]. We conclude that circRNAs maintain their functions by coding and non-coding RNAs.

This review summarized two key functions of circRNAs as sponges and RBPs (Fig. 6). In summary, sponging is a function whereby circRNAs directly interact with miRNAs, whereas RBPs combine circular RNAs to proteins with specific enzymes activity. Recent studies have focused on circRNAs that sponge miRNAs and endogenously compete with target genes to activate signaling pathways to promote or suppress BC. NOTCH, Wnt-β-catenin, EMT, and PI3K/ARK are well-known signaling pathways activated by circRNAs.

In contrast, few studies have elucidated the mechanisms by which circRNAs regulate BC progression by binding to proteins. CircRNAs induce protein degradation. Ubiquitination is a typical PTM process achieved by E1, E2, and E3 enzymes that sequentially catalyze activation, conjugation, and ligation reactions, respectively, leading to the covalent attachment of ubiquitin, usually to lysine residues of substrate proteins [137]. CircRNAs function regulate BC progression through ubiquitination; for example, circWSB1 and circKDM4B are ubiquitinated by USP10 ubiquitin ligase. USP10 ubiquitin ligase is important for the ubiquitination and regulation of BC (Fig. 2). However, the mechanism by which circRNAs regulate BC (especially TNBC) by binding to proteins requires further investigation.

Furthermore, more attention should be devoted to understanding the relationship between TNBC and circRNAs as sponges and RBPs. TNBC is an aggressive subtype that is resistant to classic BC therapies, such as paclitaxel or trastuzumab, and is hard to be operated and shows a poor prognosis [86]. It accounts for 10–20 % of all BC subtypes. TNBC is more commonly diagnosed in young women aged <50 years. The median time to death and survival after diagnosis for TNBC patients is approximately 4.2 and 10 years, respectively, while the rates for other BC subtypes are 6 and 18 years, respectively.

Proteolysis-targeting chimeras modulate protein concentrations at the post-translational level by cooperating with the ubiquitin-proteasome system. This may enable circRNA regulation at the protein level.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

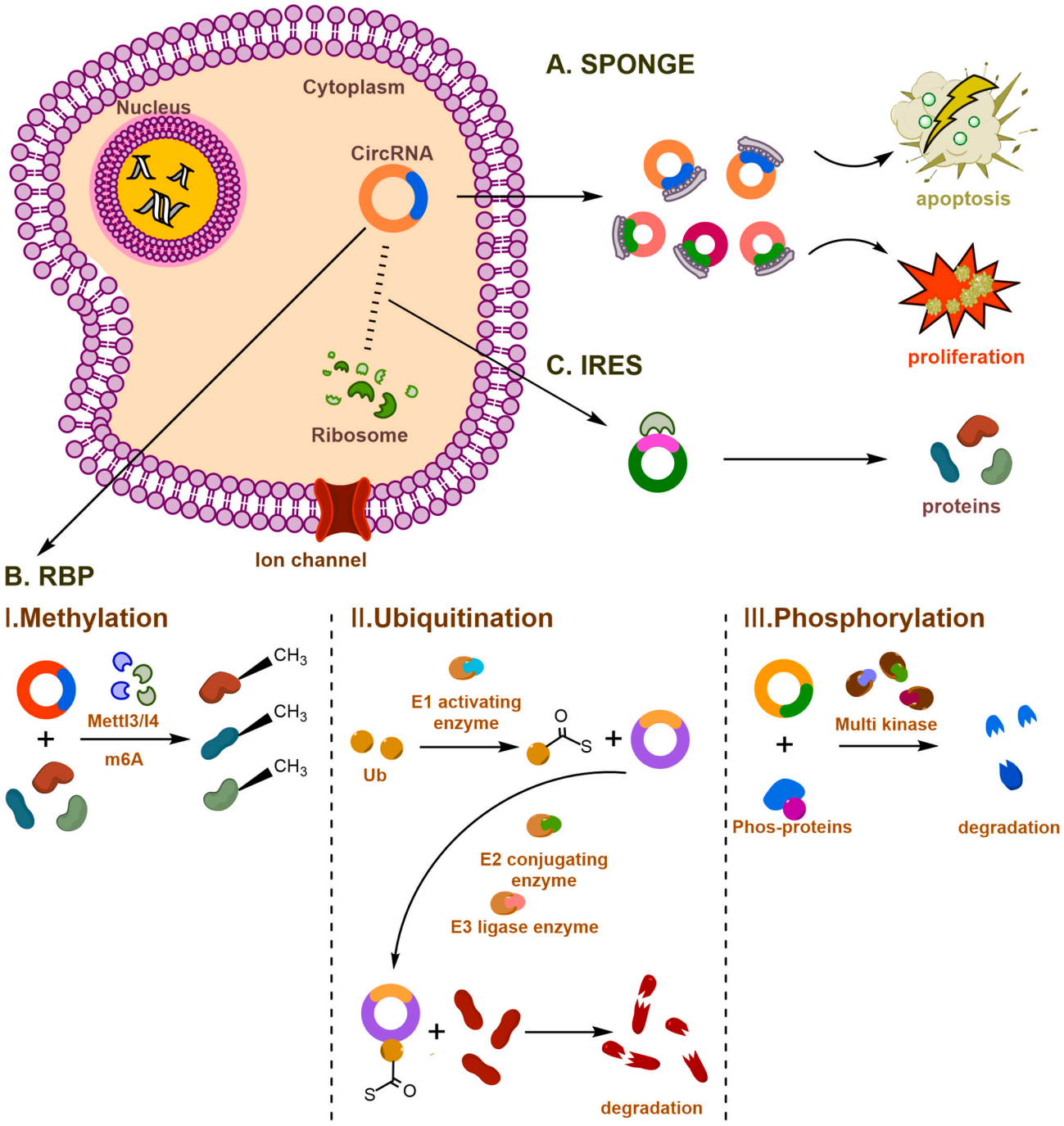

Fig. 6. A: CircRNAs act as sponge to affect BC proression. B. I: m^{6}A induces methylation activities and comprises two individual proteins: methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14). II: Ubiquitin is the progression that E1 catalyzes the formation of a covalent thioester bond between the catalytic cysteine and the di-glycine motif on the C-terminus of ubiquitin by a magnesium ion and ATP and is delivered to E2. E3 binds to E2 ubiquitin and facilitates binding to the target protein. III: Tyrosine kinase, MAP kinase, cadherin-catenin complex, and cyclin-dependent kinase are major players in the cell cycle and deregulation of phosphorylation-dephosphorylation cascade. C: CircRNAs were detected the internal ribosome entry site (IRES) to facilitate cap-independent translation.

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CRediT authorship contribution statement

Jing Zhu: Writing – original draft. **Qian Li:** Data curation, Funding acquisition, Writing – review & editing. **Zhongping Wu:** Formal analysis, Visualization. **Wei Xu:** Formal analysis, Writing – review & editing. **Rilei Jiang:** Conceptualization, Data curation, Project administration, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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