

Circular RNAs in Cancer

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Circular RNAs (circRNAs) are a class of single-stranded closed RNA molecules that are formed by precursor mRNA back-splicing or skipping events of thousands of genes in eukaryotes as covalently closed continuous loops. High-throughput sequencing and bioinformatics approaches have uncovered the broad expression of circRNAs across species. Their high stability, abundance, and evolutionary conservation among species points to their distinct properties and diverse cellular functions as efficient microRNAs and protein sponges; they also play important roles in modulating transcription and splicing. Additionally, most circRNAs are aberrantly expressed in pathological conditions and in a tissue-specific manner such as development and progression of cancer. Herein, we highlight the characteristics, functions, and mechanisms of action of circRNAs in cancer; we also provide an overview of recent progress in the circRNA field and future application of circRNAs as cancer biomarkers and novel therapeutic targets.

Circular RNAs (circRNAs) are endogenous RNAs that can form between a downstream 3' splice site and an upstream 5' splice site in a linear precursor mRNA (pre-mRNA)¹ and are transcribed by RNA polymerase II with the same efficiency as linear RNAs.² Advances in RNA sequencing (RNA-seq) and bioinformatics tools have resulted in the discovery and identification of various circRNAs and uncovered their important roles. First, recent reports have indicated that the expression of certain circRNAs is highly specific to cell type and/or developmental stage.^{3,4} Second, circRNAs lacking 3' termini are resistant to degradation by exonuclease RNase R and are more stable than associated linear mRNAs;¹ therefore, a higher concentration of circRNAs than linear mRNAs is present in quiescent and post-mitotic cells.⁵ Additionally, because of their high level of stability in blood and other body fluids, circRNAs are considered as potential biomarkers for cancer risk prediction. Third, genome-wide analyses have indicated high levels of evolutionary conservation and abundance of circRNAs across species.^{6,7} Additionally, circRNAs might act as miRNA sponges or competing endogenous RNA, bind and sequester proteins, and modulate splicing.^{1,8} Thus, circRNAs are significant in cancer pathogenesis with great potential as biomarkers for cancer, and they are likely involved in many of the hallmarks of cancer.⁹ Herein, we will highlight the critical roles of circRNAs from a cancer perspective, including their possible role as therapeutic targets in cancer.

Landscape of circRNAs

Biogenesis of circRNAs

circRNAs are derived from pre-mRNAs, and thus modulation of circRNA biogenesis may also require the canonical spliceosomal machinery.¹⁰ However, the mechanisms of action of circRNA biogenesis are not fully understood. circRNAs can originate from exons of coding regions or from 3' UTR, 5' UTR, antisense RNAs, intergenic regions, and introns.^{11,12} Among them, circRNAs in human cells are mainly derived from single or several exons, the so-called exonic circRNAs (ecircRNAs)¹⁰ that account for over 80% of identified circRNAs.¹¹ Although alternative splicing, in particular exon skipping, is considered as a major modulator of circRNA production, the main mechanism by which circRNAs are formed remains elusive. Additionally, circRNAs may be different from canonical splicing of linear RNAs; a single gene locus may produce a variety of circRNAs through alternative gene locus back-splice site selection.^{11,13} Up to now, three other types of circRNAs have been identified by high-throughput sequencing: circular intronic RNAs (ciRNAs), which contain introns only; exon-intron circRNAs (EciRNAs), which contain both introns and exons; and tRNA intronic circRNAs (trcRNAs), which can form stable circRNA via pre-tRNA splicing.¹⁰

Biological Functions of circRNAs

RNA-seq analyses have helped to identify numerous circRNAs in several model organisms with diverse cell types,¹⁴ and some endogenous circRNAs contain internal ribosome entry site elements and AUG sites.¹⁵ However, there is currently limited evidence for their translation *in vivo*,⁶ and the biological roles of most circRNAs remain unknown.^{10,16} Recent studies have shown that circRNAs can function as miRNA sponges and modulators of transcription; few circRNAs can be translated into peptides or proteins, implying that circRNAs can modulate the expression of gene at multiple levels.

<https://doi.org/10.1016/j.omtn.2019.02.005>

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circRNAs Can Function as miRNA Sponges

miRNAs can modulate gene expression via direct base pairing to target sites within mRNAs and are known to be involved in multiple biological and pathological processes, including cancer.^{9,17–20} Most circRNAs are predominantly located in the cytoplasm,¹ suggesting that circRNAs may act as competitive endogenous RNAs and modulators of miRNA activity by competing for miRNA-binding sites.^{16,21} Li et al.²² indicated that circRNA itchy E3 ubiquitin protein ligase (cir-ITCH) suppressed tumor growth by acting as a miRNA sponge and increased the level of ITCH. Chen et al.²³ reported that circPVT1 might stimulate cell growth by playing as a sponge for members of the miR-125 family.¹⁶ Importantly, some studies have indicated that ciRS-7, which may act as a designated miR-7 inhibitor or sponge by reducing miR-7 activity and increasing levels of miR-7-targeted transcripts, has conceptually changed the mechanistic understanding of miRNA networks.²⁴ *In situ* profiling studies indicated that there was a remarkable overlap in expression of ciRS-7 and miR-7 in the mouse brain, suggesting that the majority of brain-expressed miR-7 was tethered to ciRS-7.²⁴ Hence, the abundant ciRS-7/miR-7 correlation can contribute to the cellular pool of available RNA-induced silencing complex components.²⁴ Consequently, modulation of miRNAs and miRNA activity generally may be less pronounced in ciRS-7/miR-7-expressing tissues.²⁴ However, most circRNAs could have functions other than modulating miRNAs.^{16,25}

circRNAs Can Function as Modulators of Transcription

circRNAs are suggested to be restricted to the nucleus,¹ which is similar to the observation of the nuclear restriction of linear RNAs containing retained introns, and form a large number of post-transcriptional modulators.^{26,27} In contrast with circRNAs from back-spliced exons, ciRNAs can associate with the nuclear insoluble fraction and also have little enrichment for target sites of miRNAs.²⁸ Significantly, knockdown of such RNAs might lead to reduced expression of their parent genes, eliciting one potential role for ciRNAs as positive modulators of RNA polymerase II (Pol II) transcription.²⁸ Additionally, they also found that ci-Ankyrin Repeat Domain 52 (ci-ANKRD52), one abundant such RNA, can interact with the elongation Pol II complex and largely accumulates at transcription sites, which stimulates transcription of its parental gene ANKRD52.²⁸ Li et al.²⁹ also identified that the EICiRNA-U1 small nuclear ribonucleoprotein (snRNP) complexes between U1 snRNP and EICiRNAs, a special class of circRNAs, which might hold factors such as U1 snRNP through RNA-RNA interaction, could further interact with the Pol II transcription complex at the promoters of parental genes to stimulate gene expression.

circRNA Can Associate with Protein Binding

circRNAs may be involved in other physiological processes by protein binding as protein decoys or sponges. The best experimentally supported example of a circRNA protein sponge is derived from the mannose-binding lectin (MBL) locus.¹⁶ Importantly, modulation of MBL levels significantly contributes to the biogenesis of circMBL, and this effect is dependent on the MBL binding sites.³⁰ In cancer, circFOXO3 might modulate the expression of its binding

proteins through regulation of protein-protein interactions.^{7,31} circ-FOXO3 was found to bind both p53 and MDM2, and enhance breast cancer cell sensitivity to cisplatin and doxorubicin.³¹ Schneider et al.³² focused on IMP3 (IGF2BP3 [Insulin-Like Growth Factor 2 Binding Protein 3]), a RNA-binding protein and known tumor marker, to investigate circRNPs with a specific protein component. They suggested that specific circRNP families exist defined by a common protein component. Both of these studies demonstrated dynamics of circRNA-protein interaction in various tissues and cancer.

circRNAs in Hematological Malignancies

RNA-seq approaches have been frequently applied to transcriptome studies, especially deep sequencing of RNA from biological samples for investigating and cataloguing alterations in the expression and structure of transcriptomes.³³ RNA-seq has identified thousands of circRNAs with tissue- and developmental stage-specific expression, and circRNAs are also abundantly expressed in the hematopoietic compartment.³⁴

circRNAs in Hematopoietic Compartments

circRNAs in Platelets. Platelets are small, translationally competent, circulating blood cells derived from megakaryocytes³⁵ that have critical roles in hemostasis, angiogenesis, and wound healing.³⁶ Platelets are capable of pre-mRNA splicing into mature mRNAs.³⁵ Alhasan et al.³⁷ found that circRNAs are significantly enriched in platelets, where they are generated by exon back-splicing compared with nucleated cell types. Several distinct circRNAs were identified in platelets by using RNase R to selectively remove linear transcripts, and the relative proportion of circRNAs in cultured megakaryocytes is significantly lower compared with mature platelets.³⁸

However, there are limited studies on circRNA using primary patient samples in hematopoietic malignancies, and gaining further insight into the biology of circRNAs in platelets may require knowledge of how circRNA transcripts are formed in platelets and interact with miRNAs and mRNAs.³⁸

circRNAs in Exosomes. circRNAs are packaged and released in vesicles (exosomes and microvesicles) derived from platelets (Figure 1).^{17,39–41} circRNAs are more abundant and widely expressed in exosomes compared with cells.⁴² Sorting of circRNAs to exosomes can be modulated by changes of associated miRNA levels in producer cells, and thus biological activity can be transferred to recipient cells (Figure 1).¹² circRNAs were also observed in secreted extracellular vesicles and could be transferred to exosomes in KRAS mutant colorectal cancer cells.⁴²

circRNAs in Whole Blood. Recent studies have provided evidence that circRNAs are enriched in human peripheral whole blood,⁴³ and circRNAs in blood components or whole blood might be useful as a biomarker.⁴⁴ Qian et al.⁴⁴ demonstrated wide and abundant circRNA expression in human peripheral blood mononuclear cells (PBMCs), which is comparable with the circRNA landscapes in

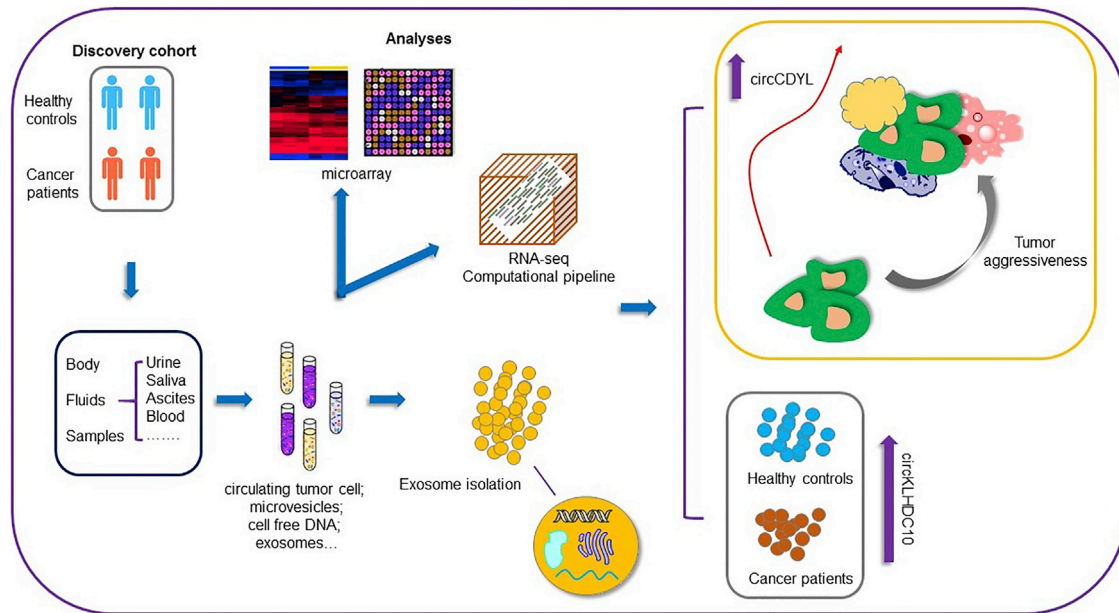


Figure 1. The Experimental Scheme of the Study

The discovery cohort was composed of healthy controls and cancer patients. circKLHDC10 and circCDYL are isolated from exosomes and profiles from RNA-seq analyses and a computational pipeline (see text for details).

human whole blood. They also found that there is a difference in circRNA expression in PBMCs from patients with active tuberculosis compared with healthy controls.⁴⁴ Zhao et al.⁴⁵ analyzed peripheral blood circRNAs of patients with coronary artery disease (CAD) and control individuals by RNA microarray. They identified five circRNAs that were all increased in the CAD group, and hsa-circ-0124644 had the largest area under the curve.⁴⁵

circRNAs from Translocations Have Oncogenic Function

Guarnerio et al.⁴⁶ have shown that circRNAs may be derived from transcription of fusion genes generated by chromosomal translocations.¹⁶ They found that circRNAs derived from multiple tumor-associated translocations, including mixed lineage leukemia (MLL)-AF9 in acute myeloid leukemia (AML) and promyelocytic leukemia-retinoic acid receptor- α (PML-RARA) in promyelocytic leukemia, and named these fusion-circRNAs (f-circRNAs). Importantly, they found that f-circRNAs (f-circPR and f-circM9) may promote cell viability, and contribute to cellular transformation and resistance upon therapy, suggesting that these f-circRNAs are biologically active and exert pro-proliferative and pro-oncogenic activities.⁴⁶ Additionally, knockdown of MLL-AF9-derived f-circRNAs stimulated apoptosis and increased p27 and p21 expression in THP1 cells, suggesting that f-circRNAs may also be significant for cell viability.⁴⁷

circRNAs in Malignant Tumors

To consider possible roles of circRNAs in various aspects of tumor biology, we consider existing knowledge in the context of hallmarks of cancer.^{9,48}

circRNAs in the Hallmarks of Cancer

Sustaining Proliferative Signaling. circRNAs may serve as important regulators of cancer development and sustained proliferative signaling. One of the best experimental examples is circ-FOXO3, which has decreased expression in tumors and might affect FOXO3, p53, and PUMA expression.⁷ Silencing endogenous circ-FOXO3 might produce an opposite effect, while ectopic circ-FOXO3 suppressed tumor progression and extended mouse life-span.⁷ Cells expressing circ-FOXO3, FOXO3, and FOXO3P formed smaller tumors than the control cells, and this inhibitory effect might be because of decreased formation of blood vessels.⁴⁹ Alternatively, the circ-FOXO3-p21-CDK2 (cyclin-dependent kinase 2) ternary complex formation might arrest the role of CDK2, and hence suppress the progression of the cell cycle.⁵⁰ By integrating bioinformatics analyses of altered circRNAs and focal copy-number variations in lung adenocarcinoma (LAC), Qiu et al.⁵¹ identified a proto-oncogenic circRNA (circ-PRKCI) that was one of the most frequent genomic aberrations in multiple cancers and might stimulate proliferation and tumorigenesis of LAC. Wang et al.⁵² also reported that hsa_circ_0014717, which is decreased in colon cancer cells, could suppress tumorigenesis by stimulating the expression of p16 (Figure 2).

Evasion of Growth Suppressors and/or Impairment of Differentiation Signals. Tumor suppressor genes generally encode proteins that can suppress tumor growth; however, loss of one or more of these “brakes” may contribute to the progression of various cancers. In addition to these mechanisms, circRNAs can help tumor suppressors to control cancer cell growth. The overexpression of circC3P1

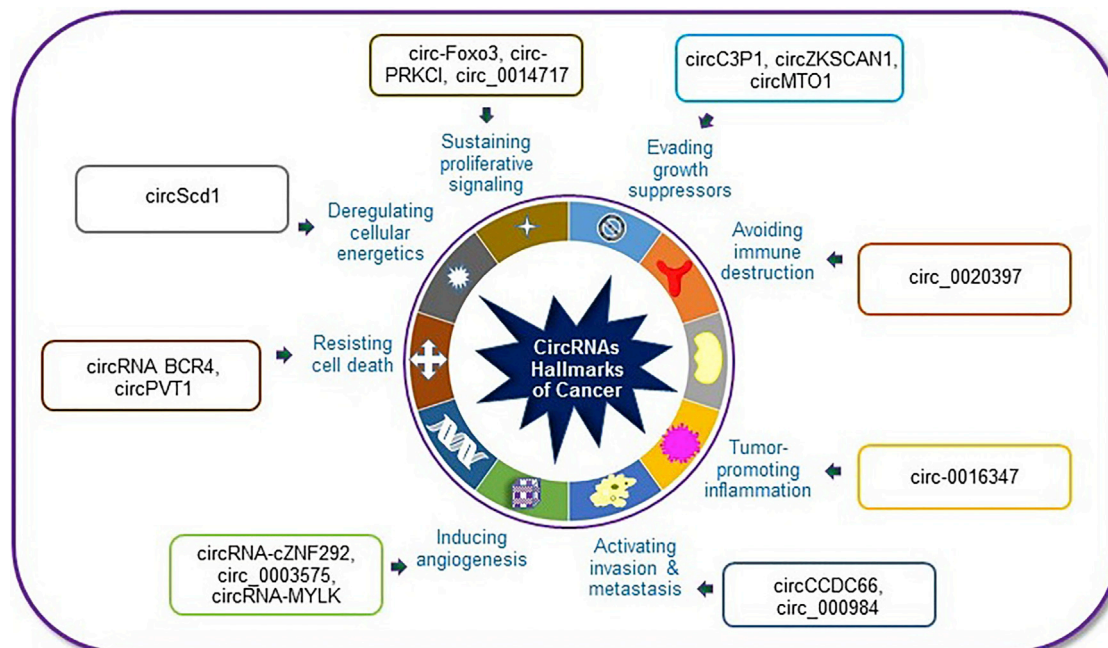


Figure 2. The Role of circRNAs Is Correlated with Hallmarks of Cancer

circRNAs have been indicated to contribute to various aspects of cancer progression (see text for details). (Adapted from Bach *et al.*⁹)

significantly suppressed the proliferation, migration, and invasion of hepatocellular carcinoma (HCC), and circC3P1 might trigger the expression of PCK1 by sponging miR-4641 in HCC cells.⁵³ Silencing both zinc finger with KRAB and SCAN domain 1 (ZKSCAN1), a zinc-finger family gene, and circZKSCAN1 could stimulate cell proliferation and tumor growth.⁵⁴ They also demonstrated that ZKSCAN1 mRNA mainly modulated cellular metabolism, whereas circZKSCAN1 contributed several cancer-associated signaling pathways, eliciting the critical role of ZKSCAN1 mRNA and circRNA in HCC cells.⁵⁴ Han *et al.*⁵⁵ showed that circMTO1 can suppress HCC progression by acting as a sponge of oncogenic miR-9 to stimulate the expression of p21, eliciting that circMTO1 could be a potential target for HCC treatment (Figure 2).

Avoiding Immune Destruction. The critical roles of miRNAs and long non-coding RNAs (lncRNAs) in tumor immunity are well reported,^{9,17} suggesting that circRNAs also participate in antitumor immunity through the circRNA-miRNA-mRNA axis.⁵⁶ Xu *et al.*⁵⁶ described an interaction between miRNAs and circRNAs, which can affect tumor immunity. hsa_circ_0020397 suppressed miR-138 activity as examined through the expression of miR-138 target telomerase reverse transcriptase (TERT) and Programmed Death-Ligand 1 (PD-L1).⁵⁷ They suggested that PD-L1 is upregulated because of the high-level expression of hsa_circ_0020397, and thus can interact with PD-1 to stimulate cancer immune escape. Yang *et al.*⁵⁸ also observed that ectopic circ-AMOTL1 can enhance protein levels of STAT3, which plays a significant role in tumor-mediated immune suppression. Together, these studies demonstrate that the

change in circRNA expression can contribute to the effect of immune checkpoint therapy.⁵⁶

Enabling Replicative Immortality. Tumor cells are known to have much greater replicative potential compared with normal cells.⁹ DNA replication is described as the process of producing two identical replicas from one original DNA molecule, and circRNAs enriched in the nucleus can subsequently interact with the opposite strand of its genomic DNA through base pairing during this process.¹¹ Consequently, they can form a DNA-RNA triple helix affecting DNA replication.¹¹ However, consistent findings for this hypothesis and hallmark are still lacking.

Tumor-Promoting Inflammation. Many studies have described an association between inflammation and cancer.^{17,18,59} The critical roles of non-coding RNAs (ncRNAs), including miRNAs,¹⁷ lncRNAs,⁹ and circRNAs, were subsequently demonstrated in many cancer cells. Bahn *et al.*⁶⁰ found 422 circRNAs in human saliva through bioinformatics analyses and carried out a gene ontology analysis of the genes overlapping putative circRNAs in human chronic fatigue syndrome. They found a highly enriched number of closely correlated categories, such as inflammatory response, chemotaxis, establishment of T cell polarity, or integrin-mediated signaling pathway, indicating that these salivary circRNAs are involved in inflammatory responses and intercellular signaling.^{60,61} Alternatively, caspase-1 can proteolytically activate inflammatory cytokines such as IL-18 and IL-1 β , which might contribute to the formation of an inflammatory micro-environment.^{62,63} Additionally, caspase-1 has higher expression in



osteosarcoma (OS) tissues compared with non-tumor tissues.⁶² Taken together, Jin et al.⁶² found that the involvement of caspase-1/miR-214/circ-0016347 in inflammation-associated mechanisms in the development of OS is potentially significant for effective treatment.

Activation of Invasion and Metastasis. Human circRNAs have been identified to contribute to tumor metastasis and invasion. Several well-studied circRNAs are specifically expressed in metastatic tumor cells. Hsiao et al.⁶⁴ investigated numerous circRNAs specifically enhanced in cancer cells from matched tumor colorectal and normal tissue samples. Among them, they found that circCCDC66 controlled various pathological processes, including migration, invasion, and anchorage-independent growth by loss-of-function and gain-of-function studies in colorectal cancer cells.⁶⁴ Silencing of circCCDC66 suppressed cancer invasion and tumor progression in mouse models.⁶⁴ Xu et al.⁶⁵ observed that hsa_circ_000984 can function as a competing endogenous RNA (ceRNA) through competitively binding miR-106b, and significantly upregulated the expression of cyclin-dependent kinase 6 (CDK6), thus promoting a malignant phenotype of tumor cells (Figure 2).

Induction of Angiogenesis. Because hypoxia is considered an important stimulus for angiogenesis,⁶⁶ many groups have studied the effects of hypoxia on endothelial cells and determined circRNA expression. Boeckel et al.⁶⁷ found that several circRNAs were significantly modulated by hypoxia. Among them, they observed that circRNA cZNF292 had proangiogenic activities *in vitro* and was involved in the regulation of endothelial cell proliferation.⁶⁷ Li et al.⁶⁸ also described that hsa_circ_0003575 silencing might stimulate the proliferation and angiogenesis ability of human umbilical vein endothelial cells through loss-of-function experiments. Zhong et al.⁶⁹ suggested that upregulating circRNA-MYLK could stimulate the growth, metastasis, and angiogenesis in breast cancer models by modulating the vascular endothelial growth factor A (VEGFA)/VEGF receptor 2 (VEGFR2) signaling pathway (Figure 2).

Genome Instability and Mutation. Genomic instability is frequently investigated in cancer and can be related to poor prognosis of cancer patients. Generally, cancer develops by the accumulation of mutations, and some mutations are considered as driver mutations that can affect a gene or regulatory element.^{9,70} Some circRNAs are highly related to mutations and post-translational modifications in cancer. Dou et al.⁴² reported that circRNAs were downregulated in KRAS mutant colorectal cancer cells and they could be transferred to exosomes. Although Okholm et al.⁷⁰ did not observe many mutations in the short intronic flanking regions, they found that some circRNAs contain more mutations than expected. Mutations in spliceosome genes, such as U2 small nuclear RNA auxiliary factor 1, splicing factor 3 subunit b1, and serine arginine-rich splicing factor 2, are suggested to be prevalent in cancer where they can influence miRNA expression and alternative splicing.^{71,72} Similarly, mutations in these genes can affect the biogenesis of circRNA; however, definitive evidence to support this hypothesis is still lacking.¹⁶

Evading Cell Death and Senescence. Many groups have reported that circRNAs can modulate cellular stress⁷³ and significantly contribute to anti-senescence and anti-stress functions of proteins through binding these proteins in cytoplasm and preventing their nuclear translocation.⁷⁴ They also demonstrated that a new approach to halting nucleus pulposus cell death could be associated with the adenoviral administration of circRNAs. Indeed, Li et al.⁷⁵ described that circRNA BCR4 overexpression can modulate cell apoptosis and miR-101/EZH2 signaling in bladder cancer. Panda et al.³ further found that circPVT1 could regulate let-7 activity and influence expression of downstream targets; silencing circPVT1 in proliferating cells stimulated senescence (Figure 2).

Deregulating Cellular Energetics. Reprogramming of energy metabolism is considered a hallmark of cancer and has received much attention because of its role in tumor pathogenesis. Many studies have used high-throughput RNA-seq technologies to investigate the regulatory mechanism of circRNAs in cancer metabolism. Mehta et al.⁷⁶ reported that the host genes that form stroke-responsive circRNAs may participate in metabolic processes. Alternatively, some studies have indicated an important correlation between non-alcoholic fatty liver disease (NAFLD) and cancer.⁷⁷ The expression of circSCD1 was found to be significantly lower in NAFLD, whereas overexpression of circSCD1 significantly suppressed the formation of lipid droplets (Figure 2).⁷⁸ Consistently, circRNA profiling and bioinformatics modeling also suggest an important regulatory role in hepatic steatosis, the hallmark of NAFLD.⁷⁹ They further indicated that lipin 1 was recognized to mediate the transcriptional regulatory effect of circRNA on metabolic pathways.⁷⁹ However, direct evidence to describe the dynamic interaction between circRNAs and cancer energy or metabolism is lacking and needs to be examined.

Taken together, these findings demonstrate important roles of circRNAs in cancer progression through modulation of many of the hallmarks of cancer (Figure 2).⁹

circRNAs as a Novel Class of Cancer Biomarkers

RNA-seq data from the Encyclopedia of DNA Elements consortium demonstrated that circRNAs are abundant and can be specifically expressed in a cell type- and tissue-specific manner; circRNAs may distinguish different tumors compared with non-cancerous tissues or predict treatment response. circRNAs are also stable and resistant to RNA exonuclease R or RNase R. Clinically, circRNAs can be found in fluids and blood, and can be potential biomarkers for detection and surveillance.⁸ Similarly, as described above, circRNAs are enriched in exosomes, suggesting potential utility as a diagnostic marker. Several studies with solid tumors have compared the differential expression of circRNAs between adjacent non-cancerous and cancer tissues through employing microarray analysis followed by evaluation of selected circRNAs in larger cohorts.¹⁶ Kun-Peng et al.⁸⁰ investigated that circPVT1 was significantly overexpressed in OS tissues, serum, and chemo-resistant cell lines, suggesting that this circRNA can be a potential diagnostic biomarker with useful sensitivity and specificity. Using circRNA profile and bioinformatics analyses, Li et al.⁸¹

**Table 1. circRNAs and Their Putative Functions in Numerous Human Cancers**

Cancer Type and Symbol	Sample Type	Expression in Tumors	Function	Related Mechanisms	References
Hepatocellular Carcinoma (HCC)					
circC3P1	tissue	down	tumor suppressor	stimulates phosphoenolpyruvate carboxykinase 1 expression through sponging of miR-4641 in HCC cells significantly suppresses the proliferation of HCC cells	53
cSMARCA5	tissue	down	tumor suppressor	enhances the expression of TIMP metalloproteinase inhibitor 3, a well-known tumor suppressor, through sponging of miR-17-3p and miR-181-5p suppresses the proliferation and migration of HCC cells	84
hsa_circ_0067531	tissue	down	–	–	85
hsa_circ_0004018	tissue	down	–	correlates with serum alpha-fetoprotein (AFP) level, tumor diameter, and differentiation	86
circRNA_100338	tissue	up	–	functions as an endogenous sponge for miR-141-3p in HCC high expression of circRNA_100338 is closely associated with metastasis progression in HCC patients	87
circ_000839	tissue	up	–	inversely correlates with miR-200b	88
circMTO1	tissue	down	tumor suppressor	suppresses HCC progression by acting as the sponge of oncogenic miR-9 to enhance p21 expression serves as a prognostic factor for poor survival of patients	55
circZKSCAN1	tissue	down	tumor suppressor	mediates several cancer-related signaling pathways inhibits cell proliferation, migration, and invasion	54
ciRS-7	tissue	down	–	high expression of ciRS-7 is significantly correlated with hepatic microvascular invasion, AFP level, and thus partly related with the deterioration of HCC	89
hsa_circ_0001649	tissue	down	–	correlates with tumor size and the occurrence of tumor embolus	90
Breast Cancer (BC)					
circ-ABCB10	tissue	up	oncogene	circ-ABCB10 knockdown suppresses the proliferation and increases apoptosis of BC cells circ-ABCB10 is targeted by miR-1271	91
hsa_circ_0011946	tissue	up	oncogene	induces the migration and invasion of MCF-7 cells hsa_circ_0011946 sponging of miR-26a/b directly targeted replication factor C subunit 3	92
circGFRA1	cells	up	oncogene	knockdown of circGFRA1 suppresses proliferation and promotes apoptosis of BC cells circGFRA1 can function as ceRNA in BC cells through modulating miR-34a	93
hsa_circ_0001982	tissue	up	oncogene	silencing of hsa_circ_0001982 inhibits proliferation and invasion, and induces apoptosis through targeting miR-143 in BC cells	94
circDENND4C	cells	up	oncogene	increases under hypoxic conditions and decreases after knockdown of hypoxia-inducible factor-1 α induces BC cell proliferation in a hypoxic environment	95
Non-small-Cell Lung Cancer (NSCLC)					
circRNA-FOXO3	tissue	down	tumor suppressor	has a relatively higher diagnostic accuracy significantly promotes cell proliferation, migration, and invasion of NSCLC cells	96
circMAN2B2	tissue	up	oncogene	acts as an oncogenic factor in NSCLC cells through stimulating FOXK1 expression by sponging of miR-1275	97

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Table 1. Continued

Cancer Type and Symbol	Sample Type	Expression in Tumors	Function	Related Mechanisms	References
hsa_circ_0014130	tissue	up	-	may interact with five miRNAs and their corresponding mRNAs can participate in NSCLC development	98
hsa_circ_0007385	tissue	up	oncogene	significantly induces the proliferation, migration, and invasion of NSCLC may interact with miR-181	99
circ-ITCH	tissue	down	tumor suppressor	plays an inhibitory role in NSCLC progression through promoting its parental gene, ITCH, expression and suppressing Wnt/ β -catenin	100
hsa_circ_0000064	tissue	up	oncogene	silencing of this circRNA can block cell-cycle progression and promote cell apoptosis	101
circRNA_100876	tissue	up	-	related to NSCLC carcinogenesis	102
Lung Adenocarcinoma (LAC)					
circRNA_102231	tissue	up	oncogene	associated with advanced tumor, metastases (TNM), stage, lymph node metastasis, and poor overall survival of lung cancer patients Induces lung cancer cells' proliferation and invasion ability <i>in vitro</i>	103
circPRKCI	tissue	up	oncogene	functions as a sponge for both miR-545 and miR-589, and abrogates their suppression of the pro-tumorigenic transcription factor E2F7 promotes proliferation and tumorigenesis of LAC	51
hsa_circ_0013958	tissue	up	oncogene	promotes cell proliferation and invasion, and suppresses cell apoptosis of LAC functions as a sponge of miR-134, thus upregulating oncogenic cyclin D1	82
Colorectal Cancer					
circCCDC66	tissue	up	oncogene	knockdown of circCCDC66 suppresses tumor growth and cancer invasion in xenograft and orthotopic mouse models, respectively	64
circ-ITCH	tissue	down	tumor suppressor	circ-ITCH can increase the level of ITCH, which is involved in the suppression of the Wnt/ β -catenin pathway	104
hsa_circ_0000069	tissue	up	oncogene	associated with patient's age and tumor size, tumor stage, node, metastasis knockdown of this circRNA can significantly suppress cell proliferation and induce G0/G1 phase arrest of cell cycle	105
circ_001569	tissue	up	oncogene	can suppress the transcription activity of miR-145 and upregulate miR-145 target E2F5, BCL2-associated athanogene 4 and formin-like 2	106
Gliomas					
circ-FBXW7	tissue	down	tumor suppressor	positively associated with glioblastoma patient overall survival	107
circ-TTBK2	tissue	up	oncogene	acts as miR-127 sponge in a sequence-specific manner knockdown of circ-TTBK2 combined with miR-217 overexpression can suppress tumorigenesis <i>in vivo</i>	108
Osteosarcoma (OS)					
circPVT1	tissue	up	tumor promoter	knockdown of circPVT1 can weaken the resistance to doxorubicin and cisplatin of OS cells through decreasing the expression of ABCB1	80

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Table 1. Continued

Cancer Type and Symbol	Sample Type	Expression in Tumors	Function	Related Mechanisms	References
hsa_circ_001564	tissue	up	oncogene	silencing of this circRNA significantly suppresses proliferation and induces cell cycle in G0/G1 phase	109
hsa_circ_0016347	cells	–	oncogene	acts as a positive modulator of proliferation and invasion in OS cells acts as a sponge of miR-124 that upregulates the expression of caspase-1	62
hsa_circ_0009910	cells	up	oncogene	promotes carcinogenesis through promoting the expression of miR-449a target interleukin-6 receptor (IL-6R) in OS cells	110
Gastric Cancer (GC)					
hsa_circ_0000520	tissue	down	–	negatively associated with TNM stage in GC plasma	111
hsa_circ_0047905	cells	up	oncogene	acts as tumor promoter in the pathogenesis of GC	112
hsa_circ_0000745	tissue	down	–	associated with tumor differentiation the expression level in plasma correlates with TNM stage	113
hsa_circ_0000096	tissue	down	–	affects cell growth and migration in GC cells through modulating cyclin D1, CDK6, matrix metalloproteinase 2 (MMP-2), and MMP-9	114
hsa_circ_0001649	tissue	down	–	significantly correlated with pathological differentiation	115
hsa_circ_0003159	tissue	down	–	negatively associated with gender, distant metastasis, and TNM stage	116
Bladder Cancer					
circRNA-MYLK	tissue	–	oncogene	function as ceRNA for miR-29a, which can contribute to EMT and the development of bladder cancer through activating the VEGFA/VEGFR2 pathway	69
circHIPK3	tissue	down	tumor suppressor	can abundantly sponge up miR-558 to suppress the expression of heparanase may suppress angiogenesis and migration of bladder cancer cells	117
circTCF25	tissue	up	oncogene	can downregulate miR-103-3p and miR-107, increase CDK6 expression, and promote proliferation <i>in vitro</i> and <i>in vivo</i>	118
circ-ITCH	tissue	down	tumor suppressor	acts as tumor suppressor by a novel circ-ITCH/miR-17, miR-224/p21, and phosphatase and tensin homolog axis	119
Cholangiocarcinoma					
hsa_circ_0001649	tissue	down	tumor suppressor	induces cell apoptosis and suppresses cell proliferation	120
Oral Squamous Cell Carcinoma (OSCC)					
circDOCK1	tissue	–	oncogene	may function as ceRNA and support the circDOCK1/mi-196a/BIRC3 axis in OSCC cells	121
Cervical Cancer (CC)					
circRNA-000284	cells	up	oncogene	knockdown of circRNA-000284 inhibits cell invasion and proliferation directly binds to miR-506 and inhibits the activity of miR-506	122
circRNA-0023404	tissue	up	oncogene	knockdown of circRNA-0023404 significantly suppresses cell invasion and migration overexpression of circRNA-0023404 is correlated with poor prognosis in CC patients	123

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Table 1. Continued

Cancer Type and Symbol	Sample Type	Expression in Tumors	Function	Related Mechanisms	References
Epithelial Ovarian Cancer (EOC)					
circHIPK3	tissues	up	-	the expression of circHIPK3 is upregulated in EOC tissues compared with normal ovarian epithelium tissues overexpression of circHIPK3 is correlated with lymph node invasion and overall survival of patients	124

EMT, epithelial-mesenchymal transition; TIMP, tissue inhibitors of metalloproteinase

characterized hsa_circ_0004277 and suggested its function as a new biomarker for AML. Zhu et al.⁸² also found that hsa_circ_0013958 might be used as a potential non-invasive biomarker for early detection and screening of LAC, as summarized in Table 1.

Future Perspectives

Although circRNAs were previously considered as “errors” in RNA splicing, thousands of endogenous circRNAs have been identified in mammalian cells that are highly conserved, and the mystery of circRNAs has gradually been uncovered. However, there are still many issues that need to be clarified regarding the role of circRNAs. First, similar to lncRNAs, circRNAs can function as tumor suppressors or tumor promoters in human cancers. Targeting oncogenic circRNAs should ideally be carried out in a manner that does not interfere with the expression of linear mRNA.¹⁶ Second, even though circRNAs could be potential cancer biomarkers, most available circRNA biomarkers are currently not sensitive or specific enough to be applied clinically. Additional work with larger sample sets with long-term follow-up clinical information is needed for further validation.^{10,83} Third, circRNA sponges, which contain several MREs compared with conventional linear miRNA sponges containing a single MRE, could be stable and effective miRNA inhibitors.⁸³ Finally, it is important to develop a standard nomenclature system. Solving these issues will provide new insights into the role of circRNA biology in cancer.

Conclusions

In summary, there is growing evidence regarding the important role of circRNAs in tumorigenesis, but circRNA research is still in its infancy. The glimpse uncovered so far suggests that circRNA-based diagnostic and therapeutic strategies could have important roles in cancer management.

AUTHOR CONTRIBUTIONS

D.-H.B. conducted the literature review and the initial draft of the manuscript. S.K.L. and A.K.S. provided overall supervision and co-edited the manuscript.

CONFLICTS OF INTEREST

A.K.S. is on the scientific advisory board of Kiyatec and Merck, has received research funding from M-Trap, and is a shareholder in Biopath.

ACKNOWLEDGMENTS

This work is supported, in part, by the NIH (grants CA016672, UH3TR000943, P50 CA217685, P50 CA098258, and R35 CA209904), Ovarian Cancer Research Fund, Inc. (Program Project Development Grant), Mr. and Mrs. Daniel P. Gordon, The Blanton-Davis Ovarian Cancer Research Program, the American Cancer Society Research Professor Award, and the Frank McGraw Memorial Chair in Cancer Research (A.K.S.), and a National Research Foundation of Korea (NRF) grant funded by the Korean Government (NRF-2016M3A9B6903499) (to S.K.L.).

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