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The Potential of Circular RNAs as Cancer Biomarkers

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ABSTRACT

Circular RNA (circRNA) is a covalently closed RNA structure that has several proposed functions related to cancer development. Recently, cancer-specific and tissue-specific circRNAs have been identified by high-throughput sequencing and are curated in publicly available databases. CircRNAs have features that are ideal properties of biomarkers, including conservation, abundance, and stability in plasma, saliva, and urine. Many circRNAs with predictive and prognostic significance in cancer have been described, and functional mechanisms for some circRNAs have been suggested. CircRNA also has great potential as a noninvasive biomarker for early cancer detection, although further investigation is necessary before clinical application is feasible.

See all articles in this *CEBP Focus* section, "NCI Early Detection Research Network: Making Cancer Detection Possible."

Introduction

RNA molecules with a circular structure were first reported in plant viroids in 1976 (1) and in eukaryotic cells in 1979 (2). Initially deemed aberrant splicing artifacts (3), circular RNA (circRNA) was identified in mammalian cells in the 1990s (4–6). Abundance and potential circRNA functions were further characterized by high-throughput sequencing in the 2010s (7–10). Large-scale studies have implicated circRNA in disease pathogenesis, including in cardiovascular disease (11, 12), neurodegenerative diseases (13, 14), and diabetes (15).

Hematologic malignancies and solid tumors also have associated circRNAs. The first reported was Cdr1as (ciRS-7), a circRNA regulator of miR-7, a tumor suppressor in breast, lung, and brain cancers (16). Subsequently, multiple circRNAs have been reported with oncogenic and tumor-suppressive potential (17). These circRNAs have reported effects on important cancer hallmarks, including sustained proliferation, resisting cell death, angiogenesis, and metastasis (17–19). CircRNA in several known cancer signaling pathways have been identified (20–22).

With proposed roles in oncogenesis, circRNA has emerged as a novel cancer biomarker. In this review, we discuss the circRNA features that are advantageous as a biomarker and its potential clinical utility in determining prognosis, predicting treatment response, and detecting cancer noninvasively.

CircRNA biogenesis

CircRNA consists of a single-stranded RNA molecule covalently closed in a loop structure. Unlike linear RNA, circRNA lacks 5′-3′ polarity and polyadenylated [poly(A)] tails (23). Whereas linear RNA is generated by alternative exon splicing, circRNA is often formed by backsplicing the 3′ end of an exon to the 5′ end of either an upstream exon or itself (refs. 8, 24; **Fig. 1**). To facilitate backsplicing, flanking introns are typically longer than 10,000 base pairs (7, 8), although not always (25). CircRNAs typically contain one to five exons (9).

Three mechanisms for circRNA structure biogenesis have been proposed. The first is intron-pairing, in which reverse complementary sequences, often repetitive ALU elements, are paired between flanking introns to facilitate backsplicing (8, 26, 27). The second mechanism involves RNA-binding proteins (RBP) attaching to flanking introns, stabilizing intron pairs to promote circularization (28, 29). The third mechanism is exon skipping, in which an exon-containing lariat precursor formed during canonical RNA splicing is subsequently backspliced into a circular structure (30). The final circRNA product can be characterized on the basis of its composition as exonic, exon–intron, or intronic (refs. 10, 31; **Fig. 1**).

CircRNA properties and biologic functions

CircRNA has several unique qualities that facilitate its biomarker potential. CircRNA is abundantly expressed, with reported increased abundance compared with parental mRNA in eukaryotic cells (8). Millions of circRNAs have been detected by bioinformatics analyses on human tissue (32). CircRNA has also been conserved among multiple species (33). CircRNAs are predominantly cytoplasmic (4, 7, 8), although occasionally nuclear (31). Because circRNA lacks 5′ and 3′ ends, including poly(A) tails, it resists exoribonuclease-mediated degradation (refs. 34, 35; **Fig. 1**). Therefore, circRNA is more stable than its linear counterpart, which remains susceptible to RNase degradation (8). Finally, several tissue- and disease-specific circRNAs have been identified (25, 32, 36).

Multiple potential biological functions for circRNA have been proposed (**Fig. 2**). The most frequently reported function is as a competing endogenous RNA. By sponging microRNA (miRNA), circRNAs suppress interaction between miRNA and mRNA, and affected circRNA/miRNA/mRNA axes underlie oncogenic and tumor-suppressive properties (16, 36, 37). Some circRNAs sponge multiple miRNAs, for example, circITCH sponges miR-216b, miR-17, miR-214, miR-7, and miR-128 in esophageal squamous cell carcinoma (20), miR-7 and miR-214 in lung cancer (38), and miR-17 and miR-224 in bladder cancer (39).

CircRNAs also interact directly with proteins, preventing target binding and scaffolding to form larger protein complexes. One example observed in HeLa cells is circPABN1 suppresses PABN1 binding to HuR, an RBP, to inhibit translation (40). CircFOXO3 complexes with CDK2 and p21 to form a scaffold and induce cell-cycle arrest (41). CircFOXO3, unlike linear *FOXO3*, binds MDM2 and p53, inducing MDM2-mediated p53 ubiquitination to promote apoptosis in breast cancer (42).

Direct circRNA translation has also been described previously. Some circRNAs contain an open-reading frame (ORF) and have an internal ribosomal entry site (IRES) to mediate translation and compensate for lack of 5′ cap and 3′ end (43, 44). Some CircRNAs undergo multiple consecutive rounds of translation when the stop codon is not recognized within the ORF on the first read (45). Examples of

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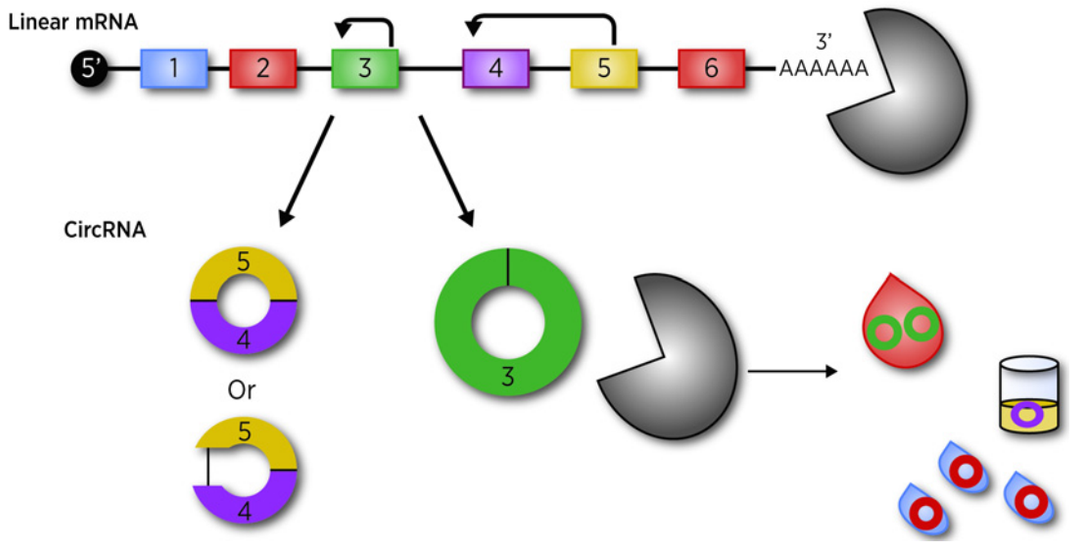

Figure 1.
Biogenesis and stability of circRNA. CircRNAs are formed from backsplicing the 5′ end of one exon to the 3′ end of another—in this figure, exon 5 onto 4 and exon 3 onto itself. Backspliced exons typically have longer flanking introns, as is the case between exon 3 and 4. The backspliced exons form covalently closed structures that may consist of one exon or multiple exons. Intronic DNA may be present as well. CircRNAs are resistant to degradation by exoribonucleases due to a lack of 3′ poly(A) tail. This enables them to be stable in plasma, urine, and saliva.

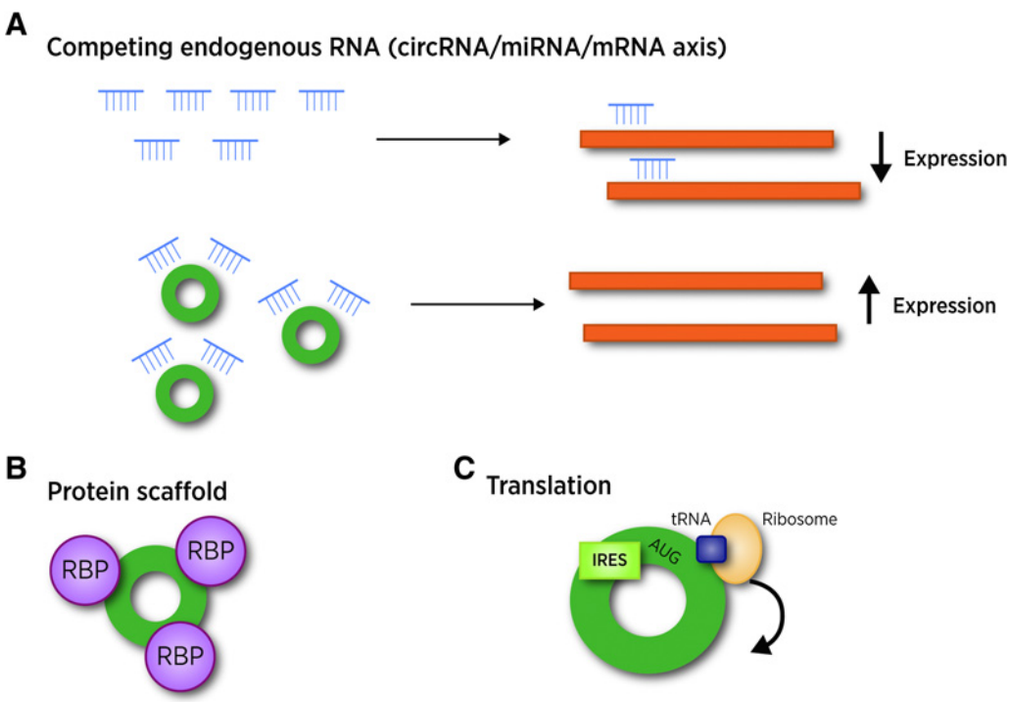

Figure 2.
Proposed circRNA biologic functions. **A,** Function as competing endogenous RNA. CircRNA can bind miRNAs that negatively regulate mRNA to increase mRNA expression. Many circRNA/miRNA/mRNA axes have been reported with potential biologic significance. **B,** Function as protein scaffold. CircRNA can help form scaffolds to stabilize protein complexes, including those involving RBPs. **C,** Function as template for translation. Some circRNAs have internal ribosomal entry sites (IRES) and open-reading frames enabling translation. CircRNAs can also undergo multiple consecutive rounds of translation.

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reported directly translated circRNAs in cancer include circβ-catenin in hepatocellular carcinoma (HCC; ref. 46), circFBXW7 in glioma (47), and circPPP1R12A in colon cancer (48). In addition, some nuclear localized circRNAs can promote parental gene transcription (31).

Materials and Methods

A literature search was performed on PubMed using terminology related to the subject of interest, including "circular RNA" and "cancer." References of the articles reviewed were also evaluated so that relevant studies missed by the keyword search were not excluded. All articles reviewed were published before May 1, 2020. Studies included in this review were selected on the basis of relevance to the topic, methodology used, and clinical applicability of proposed circRNA biomarkers.

Results

CircRNA discovery and quantification

Many circRNAs have been discovered by high-throughput sequencing. One technique uses RNA sequencing (RNA-seq) to reliably identify backspliced junctions. Alternative strategies are necessary to identify circRNA to compensate for inability to enrich polyadenylated transcripts (49). One method uses an exoribonuclease, RNase R, to enrich for circRNA (8). A downside is linear mRNA degradation, preventing mRNA quantification for further downstream analysis. One reported method to improve circRNA purification uses a lithium-based reaction buffer to prevent RNAse R stalling in guanine base-rich regions (50). Another method to improve circRNA detection efficiency is RiboZero, which uses microsphere beads to deplete ribosomal RNA, therefore enriching circRNA but also allowing further linear mRNA analysis (7, 51). Five milligrams total RNA are necessary for this method. These challenges are addressed by exome capture RNA sequencing. In this protocol, complementary capture RNA probes targeting exons of interest are hybridized with cDNA fragments (52). This method consistently detected more circRNA in cell lines and cancer tissues (53).

Another approach to circRNA discovery is microarray, which involves RNase-R–based circRNA enrichment before labeling and hybridization (54). This targeted method allows for increased certainty in circRNA annotation, for example, putative miRNA-binding sites, and requires less bioinformatics expertise and computing power than RNA-seq (55). Disadvantages compared with RNA-seq include lower sensitivity and specificity and decreased novel transcript detection. A commercially available circRNA microarray (Arraystar, Inc.) has profiled circRNA expression in multiple cancers (56–58).

Quantitative circRNA expression reported by RNA-seq or microarray allows for characterization of cancer-specific circRNAs by differential analysis between circRNA and adjacent normal tissues. CircRNAs may be upregulated or downregulated in cancer compared with normal tissue (53, 59–73). Individual cancer-specific circRNA biomarkers identified by this analysis require further validation to ascertain biologic and clinical relevance. Quantitative RT-PCR (qPCR) is commonly used to validate circRNA expression with fluorescence-based detection of amplified primers surrounding each circRNA-specific backspliced junction. Another sensitive and accurate method is droplet-digital PCR, which determines circRNA concentration by quantifying the ratio of positive to negative droplets. This technique avoids a potential issue of multiple rolling cDNA pCR products that potentially overestimates circRNA expression by qPCR (74). Droplet-digital PCR accurately detected circRNA in gastric cancer plasma and tissue (75). Another technology that measures circRNA expression is the NanoString nCounter, which hybridizes a biotinylated capture probe and uniquely color-coded reporter probe. This technique avoids enzymatic reactions and can multiplex multiple targets (76). One study using nCounter specifically detected 52 circRNAs in B-cell malignancies (77).

CircRNA expression databases

Several publicly available databases catalogue and characterize circRNAs discovered by high-throughput sequencing. These databases provide a valuable resource for further investigation into circRNA biomarkers. Overlap between databases is minimal, likely due to variability in specimens analyzed and detection platforms used (78). **Table 1** summarizes each database's unique qualities and circRNA detection tools.

CircBase compiles circRNA identified in initial landmark circRNA studies on mouse and human cell lines and lists over 90,000 unique human circRNAs (79). TCSD, a database of tissue-specific circRNAs identified in adult human, fetal human, and mouse tissues, contains more than 1 million human circRNAs (32). CircAtlas 2.0 and CIRCpedia databases detail circRNA diversity and conservation across multiple species (80, 81).

Other databases explore potential circRNA functions and downstream effects, for example, miRNA-binding sites for competing endogenous RNA. CircBank uses the same dataset as circBase to predict miRNA binding (82). CircInteractome (83) and circNet (84) both establish networks between circRNA, miRNA, and associated genes. To further understand circRNA translation, circRNAdb reports important translation elements, including ORF and IRES for 32,914 circRNAs (85). CircPro reports circRNA-coding potential (86). CircFunBase explores potential circRNA functions conserved between species (87). Other circRNA databases, including Circ2Disease (88), Circ2Traits (89), and CircR2Disease (90), explore reported phenotypic associations and physiologic relevance.

Some expression databases focus on cancer-specific circRNAs (**Table 2**). CSCD reports more than 1 million circRNA expressed in cancer-specific cell lines (91). CircRic also reports circRNAs across 935 cancer cell lines along with integrative analysis and potential drug response (92). Other databases report circRNA expression analyzed on human specimens. MiOncoCirc is a compendium of 160,120 circRNAs discovered by exome capture sequencing on cancer tissues. This database reports multiple isoforms obtained by alternative back-splicing ranked by expression (53). BBCancer details expression of six RNA types in plasma, including potential circRNA biomarkers of liver, pancreatic, and colorectal cancer (93). Although not cancer-specific, exoRbase characterizes exosomal RNA, including potential non-invasive circRNA biomarkers (94).

CircRNA clinical relevance as cancer biomarkers

CircRNA demonstrates emerging potential as a clinically useful biomarker in cancer. Tissue specificity, stability, abundant expression, and documented importance in pathways and processes that underscore cancer development are circRNA characteristics essential to its promise as a biomarker. Therefore, circRNA could improve upon classical protein-based cancer biomarkers, which are often nonspecific. Potential uses for circRNA biomarkers include prognosis, predicting treatment response, early detection, and noninvasive disease monitoring.

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Table 1. Summary of publicly available circRNA databases.

Database	Number of samples	Total human circRNA	Human/cancer specific?	Detection tool	Brief description	Ref.
Circ2Disease	N/A	237	Yes/No	N/A	CircRNA associated with disease, reports interaction with miRNA	(88)
Circ2Traits	4	1,953	Yes/No	find_circ	Associate circRNA with disease and traits	(89)
circAtlas 2.0	240	421,501	No/No	CIRI2, CIRCexplorer, DCC, MapSplice	Diversity and similarity among circRNA and expression from multiple species	(80)
circBank	34	140,790	Yes/No	Multiple sources	Comprehensive database with predicted miRNA-binding sites	(82)
circBase	20	92,375	No/No	Multiple sources	Database of circRNA identified by RNA-seq on cell lines from multiple studies	(79)
CircFunBase	N/A	3,799	No/No	N/A	Compendium of circRNA from various species with focus on reported functions	(87)
CircInteractome	34	140,790	Yes/No	N/A	Interaction between circRNA, miRNA, and potential transcripts	(83)
circNet	464	212,950	Yes/No	find_circ	CircRNA–miRNA–gene networks and reports circRNA expression	(84)
CIRCpedia v2	70	183,493	No/No	CIRCexplorer2, MapSplice	CircRNA across 6 different species	(81)
CircR2Disease	N/A	661	Yes/No	N/A	CircRNA with known association with disease	(90)
circRNADb	N/A	32,914	Yes/No	Multiple sources	Reports circRNA and possible transcripts as well as protein-coding potential	(85)
exoRBase	92	58,330	Yes/No	ACFS, find_circ	Characterize RNA (circRNA, lncRNA, mRNA) found in exosomes	(94)
TCSD	60	1,184,752	No/No	CIRI, circRNA_finder, find_circ	Tissue-specific circRNA in adult and fetal human and mouse tissue	(32)

Abbreviation: N/A, not applicable.

CircRNA has independent potential as a biomarker from its parental linear mRNA, as evidenced by differences in abundance and expression (25). In one analysis of 348 primary breast cancer specimens, correlation between circRNA and linear mRNA expression ranged between ρ −0.34 to 0.97, where 210 of 1,624 (12.9%) pairs were negatively correlated. This correlation often varied between different backspliced isoforms, for example, circESR1, with one isoform positively correlated (chr6:151842597-151880771) and another isoform negatively correlated (chr6:151880655-151944508; ref. 95).

CircRNA can also effectively differentiate between cancer subtypes. In breast cancer, circRNA-specific to triple-negative, ER-positive, and HER2-positive breast cancer have been identified. Within ER-positive breast cancer, differences between circRNA expressed in luminal A and luminal B subtypes were described previously (96). In lung cancer, circACVR2A and circCCNB1 expression effectively differentiated between squamous cell carcinoma and adenocarcinoma (97).

CircRNA prognostic biomarkers

CircRNAs with favorable and unfavorable prognostic significance have been described in multiple cancers. Numerous studies reporting prognostic circRNAs have been published recently, some of which are discussed in this review. Interestingly, circRNAs may have variable prognostic significance between cancers, for example, circZKSCAN1 that portends poor prognosis in lung cancer (98) and good prognosis in bladder cancer (99). Many prognostic circRNAs have been reported as competing endogenous RNAs, effectively functioning as oncogenes and tumor suppressors to regulate processes that drive tumorigenesis and metastasis through signaling pathways. Therefore, these biomarkers may provide eventual therapeutic targets.

Breast cancer

CircUBAP2 expression was associated with increased tumor size, advanced stage, lymph node metastasis, and comparatively worse

Table 2. Summary of publicly available cancer-specific circRNA databases.

Database	Number of samples	Total human circRNA	Cancer specific?	Detection tool	Brief description	Ref.
BBCancer	7,184	175,508	Yes	CIRI, find_circ	Blood-based biomarkers, including circRNA in liver, colorectal, and pancreatic cancer	(93)
circPro	1	2,036	Yes	CIRI2	Ribosome-associated circRNA with potential for translation into protein	(86)
CircRic	935	92,589	Yes	CIRI2, CIRCexplorer2, circRNA_finder, find_circ	CircRNA among cancer cell lines with integrative analysis and potential drug response	(92)
CSCD	228	1,394,023	Yes	CIRI2, find_circ, circRNA_finder, CIRCexplorer	Cancer-specific circRNA in cell lines and potential function	(91)
MiOncoCirc	2,000+	160,120	Yes	CIRCexplorer	CircRNA in human cancer tissues by exome capture sequencing	(53)

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overall survival in triple-negative breast cancer. CircUBAP2 was shown to interact with miR-661, a regulator of *MTA1* that has been implicated in metastasis (100). CircKIF4A expression was also upregulated in triple-negative breast cancer, correlating with worse disease-free and overall survival. Functionally, circKIF4A induces proliferation and metastasis by sponging miR-375 (101). Elevated CircAGFG1 expression indicated triple-negative breast cancer and worse overall survival. CircAGFG1 was found to increase cell migration, invasion, tumorigenesis, metastasis, and angiogenesis by sponging miR-195-5p and indirectly regulating *CCNE1* (102). High CircUBE2D2 expression also correlated with worse overall and disease-free breast cancer survival as an miR-1236 and miR-1287 sponge (103).

Conversely, high circVRK1 expression significantly correlated with improved overall survival and negatively correlated with tumor size and stage. CircVRK1 was not associated with any breast cancer subtype. Increased circVRK1 expression induced apoptosis *in vitro* (104). CircLARP4 is similarly favorably prognostic, with improved disease-free and overall survival as well as decreased tumor size and stage. Expression was comparatively decreased in breast cancer compared with normal tissue but not correlated with any subtype (105). CircLARP4 has also been identified as favorably prognostic and potential tumor suppressor in gastric cancer (106), HCC (107), ovarian cancer (108), and osteosarcoma (109).

Lung cancer

In non–small cell lung cancer (NSCLC), circSNAP47 expression resulted in decreased overall survival and significantly correlated with metastasis through the miR-1287/*GAGE* axis (110). Similarly, circZKSCAN1 exhibited decreased overall survival and higher stage (II vs. I) but not lymph node metastasis with increased expression in NSCLC. This circRNA sponged miR-330-5p, thus increasing *FAM83A* expression and regulating MAPK/ERK signal transduction (98). CircDDX42 (111) and circARHGAP10 (71) also correlated with worse NSCLC overall survival.

CircSHPRH is associated with favorable NSCLC prognosis, including improved overall survival and downregulated metastasis. MicroRNA targets include miR-331-3p and miR-338-5p (112). In lung adenocarcinoma, high circBCAR3 expression correlated with indicated improved overall survival, whereas low expression correlated with advanced stage and lymph node metastasis. CircBCAR3 sponged miR-6783-3p to increase *DKK1* expression and inhibit Wnt/β-catenin signaling (113).

In small-cell lung cancer, high expression of two circularized *FLI1* isoforms correlated with metastasis. Patients with exosomal isoform (FECR1) had higher rates of extensive-stage disease and experienced worse disease-free survival after remission. This circRNA regulated the miR-584/*ROCK1* pathway, associated with metastasis (114).

Gastric cancer

CircAGO2 expression significantly correlated with decreased gastric cancer survival. CircAGO2 interacted with HuR to diminish miRNA gene silencing and promote tumorigenesis (115). In gastric cancer, circPRMT5 functions as an oncogene, sponging miR-145 and miR-1304, thereby upregulating *myc* and decreasing overall survival when highly expressed. CircPRMT5 knockdown reduced invasion *in vitro*, which partially reversed with *myc* overexpression (116). Expression of CircLMTK2, an miR-150-5p sponge, significantly correlated with worse overall survival, higher stage, and lymph node metastasis (117). CircHIPK3 was also significantly associated with worse overall gastric cancer survival by inhibiting Wnt/β-catenin signaling (118).

PVT1 is a long-noncoding RNA often co-expressed with *myc* (119). In gastric cancer, circPVT1 was upregulated with favorable disease-free and overall survival following resection. Higher-stage tumors and those with perineural invasion expressed less circPVT1. Stratified survival analysis revealed that the subset with high circPVT1 and low linear PVT1 expression exhibited the most favorable overall and disease-free survival (120). CircYAP1, which sponged miR-367-5p to upregulate $p27^{kip}$, associated with improved overall survival in early- and late-stage gastric cancers (121).

Colorectal cancer

Two miR-7 sponges, Cdr1as and CircHIPK3 were prognostic of poor colorectal cancer overall survival (122, 123). Moreover, Cdr1as expression is prognostic for advanced tumor stage, metastatic disease, and overexpression resulted in increased *EGFR* and *RAF1* (122). CircCCDC66 expression was higher in tumor compared with precancerous polyps and indicated poor overall survival, whereas linear CCDC66 was not prognostic. CircCCDC66 overexpression increased *myc* expression (124). CircPVT1 expression significantly correlated with liver and lymph node metastases and worse overall colorectal cancer survival, unlike in gastric cancer (125). CircSLC30A7 also significantly correlated with reduced overall survival via the miR-516b/*FZD4* axis upstream of Wnt/β-catenin, a colorectal cancer developmental pathway (126). CircPPP1R12A expression also signified poor overall colon cancer survival. CircPPP1R12A reportedly encoded a protein that promoted colon cancer cell proliferation, migration, and invasion via the Hippo–Yap pathway (48).

High circCCT3 expression resulted in significantly improved overall survival following surgery and was suggested to impact *p16* downstream (127). CircACVRL1 expression significantly correlated to lower stage, decreased lymph node metastasis, and improved overall survival. Potential targets include miR-21 and miR-31 (128). CircMTO1 also carried favorable prognosis with downstream effects on Wnt/β-catenin signaling (129).

HCC

Elevated circRHOT1 expression indicated advanced disease and worse overall and recurrence-free survival following hepatectomy. CircRHOT1 had a reported direct interaction with *TIP60* to regulate *NR2F6* expression and the NOTCH2 pathway downstream (130). High circSNX27 expression significantly correlated with poor survival (68). CircSNX27 sponged miR-141-3p with downstream effects on the mTOR pathway in hepatitis B–associated HCC (131). CircZFR expression also correlated with poor survival via Wnt/β-catenin signaling (132). A circSCD isoform demonstrated significantly decreased recurrence-free and overall survival. This isoform interacts directly with *RBM3*, an RBP upregulated by hypoxia and chronic inflammation (133). Three circPTGR1 isoforms correlated with inferior HCC survival and with MET expression to mediate metastasis (134). Upregulated circCul2 expression also correlated with poor overall survival in conjunction with *Twist1*, a key mediator of epithelial–mesenchymal transition (EMT; ref.135).

CircSMARCA5 was significantly associated with decreased tumor size, grade, stage, and improved overall and recurrence-free survival after hepatectomy. This circRNA sponged miR-17-3p and miR-181b-5p to impact tumor-suppressor *TIMP3* downstream (136). CircADAMTS13 was downregulated in HCC and resulted in improved recurrence-free survival. CircADAMTS13-sponged miR-484, a mediator of hepatocyte malignant transformation (137). CircMTO1 expression also correlated with improved overall HCC survival via miR-9/*p21* (138). CircITCH, which affects Wnt/β-catenin signaling, was also

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associated with improved HCC survival (139). High CircTRIM33–12 expression also significantly resulted in improved overall survival and recurrence-free survival following surgery via miR-191/*TET1* (140).

Bladder cancer

Elevated circMYLK expression indicated worse bladder survival. CircMYLK directly bound miR-29a, thus regulating *VEGFA* expression, EMT, and RAS/ERK signaling (141). CircBPTF expression also significantly correlated with worse overall survival, and expression was higher in muscle invasive than non–muscle-invasive bladder cancer via miR-31-5p/RAB27B (142). CircTFRC was more expressed in higher-grade bladder cancer and associated with reduced survival. This circRNA sponged for miR-107 and induced EMT through TGFβ downstream (143).

Thirteen circRNAs predicted risk of progression from non–muscle invasive to muscle-invasive bladder cancer. Four of these circRNAs exhibited higher expression than corresponding linear transcripts. CircHIPK3 and circCDYL significantly demonstrated decreased progression risk, which was independent of parental linear transcript expression (144). CircITCH expression is associated with improved bladder cancer survival. Reported miRNA targets are miR-17 and miR-224, which regulate *p21* and *PTEN* to drive tumor progression (39). CircSLC8A1 also reportedly regulated *PTEN* by sponging miR-130b and miR-494 to reduce bladder cancer progression (145). CircMTO1 expression significantly correlated with improved overall and disease-free bladder cancer survival. *In vitro*, circMTO1 reduced bladder cell invasion by sponging miR-221 and inhibiting EMT (146). CircUBXN7 expression also results in significantly improved overall survival, whereas linear UBXN7 mRNA is not prognostic. CircUBXN7 suppressed miR-1247-3p, thus promoting *B4GALT3* expression (147). A poor prognostic marker in lung cancer, high circZKSCAN1 expression correlated with improved overall and disease-free bladder cancer survival via miR-1178-3p/*p21* (99). In muscle-invasive bladder cancer circLPAR1 expression correlated to improved disease-specific survival and targeted four unique miRNAs (148).

Prostate cancer

Compared with castration-resistant prostate cancer, circAURKA was upregulated and circAMACR was downregulated in neuroendocrine prostate cancer, a rare and aggressive subtype (53). High circHIPK3 expression also indicated worse prostate cancer prognosis and advanced tumor stage through interaction with the miR-193a-3p/*MCL1* axis (149). In one study abundance or paucity of overexpressed circRNAs was a poor prognostic factor. Here, a circRNA index (CRI) was calculated to reflect the number of overexpressed circRNAs. In an intermediate risk localized prostate cancer cohort, the combined subset of patients with the lowest and highest CRI quartiles had worse biochemical recurrence-free interval than patients with intermediate CRI (87).

Higher CircITCH expression was associated with lower stage, decreased lymph node metastasis, and improved disease-free and overall survival (150). CircMTO1 expression also correlated to favorable prostate cancer disease-free and overall survival and targeted miR-17-5p (151).

Ovarian cancer

Elevated CircHIPK3 expression signified worse disease-free and overall ovarian cancer survival, higher FIGO stage, and lymph node invasion (152). CircPIP5K1A expression also significantly correlated with worse overall ovarian cancer survival via miR-661/*IGFBP5* (153). Elevated circABCB10 expression indicated higher grade, larger tumor size, and worse overall survival. Potential miRNA targets include miR-1271, miR-1252, and miR-203 (154). High circFAM53B also resulted in decreased overall survival. This circRNA sponged miR-646 and miR-647 to increase *VAMP2* and *MDM2* expression, respectively (155).

CircPLEKHM3 sponged miR-9 to increase wild-type *BRCA1*, resulting in improved overall and recurrence-free survival. Other miR-9 targets included *KLF4* and *DNAJB6*, with β-catenin and AKT1 downstream (156). CircITCH is favorably prognostic in ovarian cancer via miR-145/*RASA1* (157).

CircRNA predictive biomarkers

CircRNAs have also been reported that predict response and resistance to multiple cancer treatment modalities. Therefore, they may prove clinically valuable for personalizing treatment to achieve optimal outcomes with fewer toxicities.

Radiation

Analysis of esophageal squamous cell carcinoma radioresistant and radiosensitive cell lines revealed 74 differentially expressed circRNAs, of which nine were validated by qPCR. Several circRNA downregulated in resistant cells affected Wnt signaling downstream (158). Further evidence of circRNA conferring radiation resistance through this pathway includes circDCAF8-sponging miR-217 to regulate *Wnt3* in radioresistant esophageal cancer cells (159). In cervical cancer HeLa cells, RNA-seq on irradiated cells identified 153 differentially expressed circRNA targets, most commonly affecting MAPK signaling (160). In NSCLC, Cdr1as was shown to inhibit radioresistant effects of miR-1246 (161), and circMTDH4 promoted radiation resistance in lung cancer cell lines through the miR-630/*AEG-1* axis (162).

Predictive circRNAs have also been identified in irradiated cancer tissues. In radiosensitive and radioresistant colon cancer tissues, circCCDC66 expression correlated with resistance whereas its target, miR-338-3p associated with radiosensitivity. *In vitro*, circCCDC66 expression increased with higher radiation doses, whereas CCDC66 knockdown induced apoptosis through caspase-3 (163). In nasopharyngeal cancer, circHIPK3 expression was increased in radioresistant tissues (164). CircMALAT1 expression was also increased in radioresistant nasopharyngeal tissue and cell lines via miR-9/*PDGFRB* (165). Also in nasopharyngeal cancer, curcumin generated radiosensitization through circRNA regulation (166). CircAKT3 has been associated with protein translation to decrease glioblastoma radioresistance (167).

Chemotherapy

Platinum-based chemotherapies induce DNA damage to kill tumor cells. CircPVT1 is implicated in cisplatin resistance in gastric cancer, NSCLC, and osteosarcoma. In lung adenocarcinoma, circPVT1 was upregulated in cisplatin and pemetrexed resistant cancer cells through the miR-145-5p/*ABCC1* axis, and higher *ABCC1* expression resulted in worse prognosis (168). CircPVT1 was also associated with doxorubicin and cisplatin resistance in osteosarcoma by upregulating *ABCB1*, previously implicated in drug efflux and multidrug resistance (169). Cdr1as has been associated with cisplatin resistance and sensitivity. In lung cancer cells, Cdr1as was associated with cisplatin and pemetrexed resistance, which was reversed with EGFR overexpression (170). Alternatively in bladder cancer, Cdr1as expression demonstrated improved cisplatin response and induced apoptosis via miR-1270/*APAF1* (171). In ovarian cancer, Cdr1as was downregulated in cisplatin-resistant tissue and directly interacted with miR-1270 to

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increase *SCAI* (172). CircAKT3 has also been associated with cisplatin resistance in lung cancer via miR-516b-5p/*STAT3* (173) and in gastric cancer via miR-198/*PIK3R1* (174). CircPGC also increases cisplatin resistance via the STAT3 pathway in NSCLC by sponging miR-296-5p (175). CircFNTA activates *KRAS* signaling through interaction with miR-370-3p to inhibit apoptosis and cisplatin response and is regulated by androgen receptor (176). Other circRNA-mediating cisplatin resistance include circHIPK3 and circELP3 in bladder cancer (177, 178), circZFR in NSCLC (179), circEIF6 in anaplastic thyroid cancer (180), and circFN1 in gastric cancer (181). In microarray expression analysis of colon cancer cells exposed to 5-FU and oxaliplatin, resistant cells displayed 773 upregulated and 732 downregulated circRNAs. CircSATB1 was the most upregulated circRNA (182). CircCCDC66 was more highly expressed in oxaliplatin-resistant colorectal cancer cells, with expression induced by *DHX9* phosphorylation after oxaliplatin treatment (183). CiRS-122 generated oxaliplatin resistance in colorectal cancer cells by exosomal delivery via the miR-122/*PKM2* axis (184). In HCC, circFBXO11 induced oxaliplatin resistance by targeting miR-605/*FOXO3* to promote ABCB1 transcription (185). Conversely, CircFAM114A2 promotes oxaliplatin sensitivity in gastric cancer cells by sponging miR-421 to upregulate *ATM* expression (186).

Doxorubicin is an anthracycline topoisomerase inhibitor. Resistant breast cancer tissues and cells demonstrated higher circPRELID2 expression via miR-7-5p/*RAF1* to upregulate downstream *MEK*/*ERK* signaling (187). CircLARP4 is associated with enhanced doxorubicin sensitivity in breast cancer (105) and osteosarcoma but not methotrexate sensitivity (109). CircKDM4C is another potential biomarker of doxorubicin sensitivity via the miR-548p/*PBLD* axis (188).

CircRNAs have predicted taxane sensitivity and resistance. In analysis of paclitaxel-resistant lung cancer cells, 11,281 circRNAs were differentially expressed with 2,909 circRNAs upregulated (189). In lung adenocarcinoma, circARFGEF2 was implicated in miR-326–mediated docetaxel resistance (190). CircPVT1 expression in gastric cancer tissues predicted paclitaxel resistance. *In vitro*, circPVT1 inhibited miR-124-3p to increase *ZEB1* expression to promote EMT (191). In breast cancer, circABCB10 expression was comparatively higher in paclitaxel-resistant tissues. In cells, circABCB10 inhibited miRNA let-7a-5p to increase expression of *DUSP7*, a MAPK inhibitor (192). CircAMOTL1 was also implicated in paclitaxel resistance in breast cancer cells by binding and inhibiting *AKT* phosphorylation (193). In ovarian cancer, circCELSR1 expression was increased in paclitaxel-resistant tissue via miR-1252/*FOXR2* (194). In nasopharyngeal cancer, circCRIM1 predicts docetaxel resistance to docetaxel via the miR-422a/*FOXQ1* axis (195). Conversely, circPTK2 expression correlates with taxane chemosensitivity in NSCLC. This circRNA sponges multiple miRNAs and enhances paclitaxel sensitivity by inhibiting miR-182-5p to regulate *GRB2, FOXO1*, and *FOXO3* downstream (196). CircFOXO3 expression reduced docetaxel resistance *in vitro* and *in vivo* and enhanced linear *FOXO3* expression (197).

CircRNA also predicts gemcitabine response in pancreatic and bladder cancer. Two studies evaluated differential circRNA expression in gemcitabine-resistant pancreatic cancer cell lines. 26 circRNAs were upregulated and 55 downregulated circRNAs in one study and 68 upregulated and 58 downregulated circRNAs in the other (198, 199). CircHIPK3 expression was higher in gemcitabine-resistant pancreatic cancer tissues. In cells, circHIPK3 sponged miR-330-5p to upregulate *RASSF1* expression (200). Conversely, circHIPK3 overexpression resensitized previously gemcitabine-resistant bladder cancer cells (201). Likewise, circSMARCA5 overexpression enhanced chemosensitivity in gemcitabine and cisplatin-treated lung cancer cells (202).

Targeted therapies

CircRNAs have also been implicated in resistance to molecularly targeted agents. Microarray-based expression analysis on two lung cancer cell lines resistant to osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), revealed 7,966 upregulated and 7,538 downregulated circRNAs. The most highly differentially expressed circRNA mediated effects on *p53* and *mTOR*, both previously implicated in resistance (203). CircCCDC66 was highly expressed in *EGFR*-mutated–resistant cell lines (204). CircCDK14 overexpression in lung cancer cells conferred resistance to gefitinib, another *EGFR*-targeting TKI, via the miR-1183/*PDPK1* axis (205). Alternatively, expression analysis on serum from gefitinib-sensitive patients with NSCLC revealed circZNF117 and circZNF91 overexpression, correlating with improved progression-free survival (206). In oral squamous cell carcinoma, circGDI2 overexpression increased sensitivity to cetuximab, an anti-EGFR antibody, by promoting apoptosis and regulating *EGFR* expression (207).

Immune checkpoint inhibition treats multiple cancers, but patients often develop resistance. In NSCLC, patients who progressed on anti–PD-1 therapy exhibited comparatively higher circFGFR1 expression. CircFGFR1 increases *CXCR4* expression, thereby reducing $CD8^+$ T-cell recruitment (208). In pancreatic cancer, four circRNAs (circUBAP2, circCLEC17A, circHIBADH, and circTADA2A) regulate CXCR4 and ZEB1, two proteins that correlated with CTLA4 and PD-1 expression (209).

Endocrine therapies

CircRNAs have been proposed that predict endocrine therapy response in breast, ovarian, and prostate cancer. Higher circCNOT2 expression in breast cancer indicated earlier progression on aromatase inhibitors, whereas linear CNOT2 was not predictive (95). CircGAPDH also induces tamoxifen sensitization *in vitro* and *in vivo* through miR-182-5p/*FOXO3* (210).

Enzalutamide is an antiandrogen that treats prostate cancer. Screening circRNAs in enzalutamide-resistant cells revealed 230 upregulated and 465 downregulated circRNAs in a highly resistant clone and 60 upregulated and 175 downregulated circRNAs in a moderately resistant clone. One downregulated circRNA, CircRBM39, is derived from a parental gene in the *U2AF65* family that regulates ARv7, previously described in enzalutamide resistance (211). CircRNA17 expression is decreased in high-grade prostate cancer and also decreases enzalutamide resistance by enhancing miR-181c-5p stability to modulate ARv7 expression (212).

Treatment side effects

CircRNAs may detect adverse treatment toxicities, including doxorubicin-mediated cardiotoxicity. CircTTN, CircFHOD, and CircSTRN3 promote protective effects of QKI against doxorubicin-induced cardiotoxicity (213). CircPan3 was also downregulated along with QKI in a model of doxorubicin cardiotoxicity, whereas miR-31-5p was upregulated (214). In a model of cisplatin-induced acute kidney injury, circZNF644 expression was upregulated via miR-494/*ATF3* with downstream effects on IL-6, a proinflammatory factor (215). High circRSF1 expression may signify radiation-induced hepatic injury by sponging miR-146a-5p to increase proinflammatory cytokines in irradiated liver cells (216). Microarray analysis for circRNA in irradiated hepatic stellate cells

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found 179 upregulated and 630 downregulated circRNAs, of which circPALLD inhibits proliferation after radiation (217).

CircRNA noninvasive detection

Perhaps the greatest cancer biomarker potential for circRNA is noninvasive detection with clinical implications for early detection and serial monitoring. Advantages of using circRNA for early cancer detection include stability, lineage specificity, conservation, and abundance. Because of exoribonuclease degradation resistance, circRNA is more stable than corresponding linear mRNA. CircRNA has been detected in exosomes, plasma, saliva, and urine (53, 218, 219). CircRNA could also potentially facilitate a more accurate diagnostic platform than circulating tumor DNA. One circulating tumor DNA early detection platform, CancerSEEK, demonstrated strong sensitivity for some cancers but inaccuracy for others, especially earlier-stage cancers (220). Utilization of cancer-specific circRNA may overcome these inaccuracies. Challenges in developing plasma circRNA-based detection assays include selecting abundantly expressed backspliced isoforms and determining clinically relevant targets, given variable expression between circRNA and parental linear transcripts (95). Nonetheless, noninvasively detected cancer-specific circRNA have been reported.

CircRNA and early detection

Several circRNA biomarkers for early cancer detection have been proposed. Sensitivity and specificity at a determined cutoff point and area under the receiver operative curve (AUC) for noninvasively detected circRNA biomarkers across several cancers are represented in **Table 3**. In NSCLC, F-circEA is generated from backsplicing *EML4–ALK* fusion gene exons. This circRNA was detected in *EML4–ALK*-positive lung cancer plasma, whereas the corresponding linear mRNA was not (221). In plasma from 153 patients with lung cancer, 83 of whom had stage I disease, circYWHAZ and circBNC2 exhibited differential expression in patients with cancer compared with healthy controls. Sensitivity and specificity AUC for lung cancer detection using both circRNA was 0.81 for the entire cohort and 0.83 for stage I patients (222). CircFARSA also has been detected in NSCLC patient plasma. Expression was upregulated in cancer and moderate correlation was observed between plasma and lung tissue circFARSA expression ($\rho = 0.64$). Sensitivity and specificity AUC for lung cancer detection was 0.71 (70). Another circRNA biomarker proposed for early lung adenocarcinoma detection is circACP6. This circRNA exhibits upregulated expression in lung adenocarcinoma, with reported sensitivity and specificity AUC 0.794 for plasma-based lung adenocarcinoma identification (69). As lung cancer does not currently have clinically useful noninvasive biomarkers for early detection, plasma circRNA biomarkers are promising.

Although serum breast cancer biomarkers exist, they are not commonly used for early detection. CircELP3 is a proposed plasma breast cancer biomarker, as expression was significantly increased compared with normal controls. In a cohort of 57 patients with breast cancer and 17 age-matched healthy controls, sensitivity and specificity AUC of circELP3 expression was 0.784, compared with CEA (AUC 0.562) and CA15-3 (AUC 0.629). Sensitivity and specificity improved to AUC 0.839 with combined circRNA and protein biomarkers (223).

One study performed RNA-seq on serum from 11 patients with colorectal cancer and healthy controls. Compared with healthy controls, colorectal cancer serum contained 257 likely cancer-specific

Table 3. Sensitivity and specificity of reported differential circRNA expression in cancer plasma compared with normal patients for early cancer detection.

Primary cancer	CircRNA	Sensitivity	Specificity	AUC	Ref.
Lung	circYWHAZ (hsa_circ_0005962) circBNC2 (hsa_circ_0086414)	77.8%	72.2%	0.81	(222)
Lung	circFARSA	Not reported	Not reported	0.71	(70)
Lung	circACP6 (hsa_circ_0013958)	75.5%	79.6%	0.815	(69)
Breast	circELP3 (hsa_circ_0001785)	76.4%	69.9%	0.784	(223)
Colorectal	circFAM71F2 (hsa_circ_0082182) circFLI1 (hsa_circ_0000370) circALDH1A2 (hsa_circ_0035445)	Not reported	Not reported	0.835	(224)
Colorectal	circCCDC66 circABCC1 circSTIL	64.4%	85.2%	0.780	(225)
Gastric	circXPO1 (hsa_circ_0001017) circNRIP1 (hsa_circ_0061276)	84.7%	96.6%	0.912	(75)
Gastric	circLMO1 (hsa_circ_0021087) circUBXN7 (hsa_circ_0005051)	Not reported	Not reported	0.773	(226)
Gastric	circRPL6	Not reported	Not reported	0.733	(227)
Gastric	circCNIH4 (hsa_circ_0000190)	41.4%	87.5%	0.60	(228)
Gastric	circSPECC1 (hsa_circ_0000745)	85.5%	45.0%	0.683	(229)
Gastric	circTATDN3 (hsa_circ_0000181)	99.0%	20.6%	0.582	(230)
Pancreatic	circLDLRAD3	57.4%	70.5%	0.67	(231)
Liver	circHPCAL1 (hsa_circ_0000976)	87.5%	84.0%	0.858 (Set 1)	(232)
	circRABGGTA (hsa_circ_0007750) circMTM1 (hsa_circ_0139897)	85.5%	89.5%	0.875 (Set 2)	
Liver	circSMARCA5	86.7%	89.3%	0.938	(233)
Liver	circSMARCA5 (hsa_circ_0001445)	71.2%	94.2%	0.862	(234)
Oral (saliva)	circBICD2 (hsa_circ_0001874) circFAM126A (hsa_circ_0001971)	92.7%	77.8%	0.922	(236)

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circRNAs, 53 of which correlated to known genes upregulated in colorectal cancer tissues. Among these, circKLHDC10 was further validated as significantly cancer-specific (218). A microarray study analyzed circRNA in plasma from 156 patients with colorectal cancer, including 66 stage I patients. 204 differentially expressed circRNA between cancer and normal plasma were identified, of which 178 were upregulated. Further qPCR identification identified two upregulated circRNAs, circFAM71F2 and circFLI1, and one downregulated circRNA, circALDH1A2, in serum from patients with stage I colorectal cancer compared with normal controls. All three circRNA biomarkers combined had the highest sensitivity and specificity for noninvasive colorectal cancer detection (224). CircRNA expression analysis in colorectal cancer patient plasma found decreased circCCDC66, circABCC1, and circSTIL expression compared with healthy controls. In a separate validation cohort, these circRNA markers yielded better sensitivity and specificity for detection than CEA. Sensitivity and specificity of the assay improved to AUC 0.855 by combining these circRNA biomarkers with CEA. These circRNAs retained diagnostic value in subanalysis of early stage, CEA-negative, and CA19-9–negative colorectal colon cancer (225).

Differential expression analysis on blood from patients with gastric cancer found 172 upregulated and 171 downregulated circRNAs, of which only 17 were differentially expressed in gastric cancer tissue. Furthermore, plasma expression of two downregulated circRNAs, circXPO1 and circNRIP1, was validated by droplet-digital RT-PCR measurement. When combined, their specificity and sensitivity AUC for diagnosing gastric cancer in serum was 0.912, which was superior to the same assay in tissue (AUC 0.779; ref. 75). A diagnostic assay with circLMO1 and circUBXN7 also distinguished patients with gastric cancer from controls. When combined with CEA, sensitivity and specificity AUC was 0.7988 (226). Individual circRNAs investigated for noninvasive gastric cancer diagnosis include circRPL6, which had downregulated expression with sensitivity and specificity AUC 0.733. When combined with protein biomarkers CEA, CA19-9, and CA72-4, AUC improved to 0.825. In patients exhibiting normal protein biomarker levels, sensitivity and specificity was inferior (AUC 0.692), indicating potential for circRNA to detect cancer underdiagnosed by conventional means (227). CircCNIH4 was also downregulated in serum and tissue from patients with gastric cancer compared with normal controls, although sensitivity and specificity for cancer detection was higher for tissue than plasma (228). Plasma circSPECC1 expression was also significantly different between patients with cancer and controls with AUC 0.683, which improved to 0.775 in combination with CEA (229). Another reported early gastric cancer detection biomarker is circTATDN3. Expression was significantly decreased in patients with gastric cancer with cutoff point sensitivity 99.0% but poor specificity at 20.6% (AUC 0.582; ref. 230).

In pancreatic cancer, circLDLRAD3 has been evaluated for noninvasive detection. In plasma from 31 patients with pancreatic cancer, circLDLRAD3 expression was upregulated compared with healthy controls. Plasma expression level correlated with CA19-9, metastasis, lymphatic and venous invasion, and stage. Independently, circLDLRAD3 had sensitivity and specificity AUC 0.67 for noninvasive detection. Combining circLDLRAD3 with CA19-9 improved sensitivity and specificity of this established pancreatic cancer protein biomarker from AUC 0.83 to 0.87 (231).

In HCC, a validated diagnostic cohort with three circRNA biomarkers, circHPCAL1, circRABGGTA, and circMTM1, was developed to distinguish patients with cancer from healthy and HCC precursor (hepatitis B and cirrhosis) control patients. This panel outperformed AFP in distinguishing HCC from non-HCC in two validation sets, and accuracy further improved with circRNAs and AFP combined. The circRNA panel also had high diagnostic accuracy in detecting small HCC tumors and AFP-negative HCC, often missed by conventional diagnostic techniques (232). In another study, circSMARCA5 expression was significantly decreased in patients with HCC compared with healthy and HCC precursor control patients. Sensitivity and specificity AUC for HCC detection compared with healthy controls was 0.938, although the assay was less specific and sensitive when differentiating HCC from precursor diseases. Sensitivity and specificity AUC of circSMARCA5 expression in patients with AFP <200 ng/mL compared with patients with hepatitis and cirrhosis was 0.847 and 0.706, respectively. Therefore, this noninvasive marker could detect patients who may not be diagnosed otherwise (233). Another circSMARCA5 expression assay also found decreased plasma expression in patients with HCC. Sensitivity and specificity AUC for HCC diagnosis compared with healthy controls, patients with hepatitis B and cirrhosis was 0.970, 0.877, and 0.743, respectively (234).

CircRNA specific to genitourinary tumors can be detected in urine. In a study supported by the early detection research network, exome capture RNA-seq on urine obtained from patients with prostate cancer detected 6,788 circRNAs, 1,092 of which were detected in prostate cancer tissue (53). In bladder cancer, circPRMT5 was detected in urinary exosomes, and higher expression positively correlated with lymph node metastasis and tumor progression (235).

Noninvasive circRNA detection can occur in saliva for head and neck cancers. In a study of 93 patients with oral cancer and healthy controls, differential expression was detected in 32 circRNA, with 12 upregulated and 20 downregulated. Two circRNAs, circBICD2 and circFAM126A, effectively differentiated between oral cancer and oral leukoplakia. These two circRNA combined demonstrated excellent sensitivity and specificity for cancer diagnosis (AUC 0.895; ref. 236).

CircRNA and disease monitoring

Another potential use for circRNA biomarkers is noninvasive monitoring for recurrent and progressive disease. When CircRNA expression normalizes postoperatively, subsequent significant changes in expression may indicate recurrent disease (223, 224, 226, 227, 236). A validated circRNA model was developed to predict postoperative recurrence in stage II and III colon cancer. Candidate circRNAs were determined by RNA-seq on resection tissue from known recurrences and nonrecurrences. Four circRNAs, circPLOD2, circAGTPBP1, circISPD, and circPRKAR1B, comprised a recurrence risk score that predicted postsurgical disease-free and overall survival, which could potentially guide decisions about adjuvant therapy (237). A model of stage III gastric cancer recurrence used four circRNAs, circTMCO3, circCDK14, circNEK6, and circLPHN2, determined by differential expression on tissue. This model's prediction of disease recurrence within 1 year had sensitivity and specificity AUC 0.711 in the validation set, which improved to 0.818 when combining circRNAs and tumor stage (238).

CircRNA may also predict progression on chemotherapy in noninvasive assays. Differential circRNA expression on plasma from gemcitabine-sensitive and -resistant patients revealed two circRNAs, circSNORD114-1 and circDCUN1D4, that predicted resistance (199). In serum exosomes derived from patients with ovarian cancer, Cdr1as expression level was significantly higher in cisplatin-sensitive patients than resistant patients (172). Therefore, circRNA biomarkers could help determine development of chemotherapy resistance in cases where progression is otherwise clinically uncertain.

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Discussion

CircRNA has emerged as an intriguing multifaceted cancer biomarker. Inherent biologic properties, including stability due to exoribonuclease resistance and potential for tissue specificity underlie the potential for using circRNA in noninvasive detection, likely its most useful application. Hundreds of potential prognostic, predictive, and diagnostic circRNA biomarkers have been described previously. Several of these, including Cdr1as, circITCH, circPVT1, and circHIPK3 are expressed in multiple cancers. Some circRNAs also have divergent implications among cancer subtypes, for example, circPVT1, which signifies good gastric cancer prognosis and poor colorectal cancer prognosis. Further studies are necessary to independently verify these trends and better understand the biological mechanisms behind each circRNA. Moreover, it remains unclear which reported circRNAs are truly tissue and cancer specific. Although specific circRNA/miRNA/mRNA interactions have been described, many circRNAs have multiple purported miRNA-binding sites and can target multiple genes. The functional relationship between circRNAs and parental mRNA needs to be further clarified, given their variable correlation. Although circRNAs offer great promise as cancer biomarkers, especially for noninvasive detection, prospective validation is necessary before clinical application is feasible.

Authors' Disclosures

A.M. Chinnaiyan reports other from LynxDx and Flamingo Therapeutics (cofounder and scientific advisory board member) outside the submitted work, as well as a patent for lncRNA IP issued to Genome Dx. No disclosures were reported by the other author.

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The Potential of Circular RNAs as Cancer Biomarkers

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