Recent progress of circular RNAs in different types of human cancer: Technological landscape, clinical opportunities and challenges (Review)

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Abstract. Circular RNAs (circRNAs) are a novel class of endogenous non-coding RNAs that have been recently regarded as functionally active. CircRNAs are remarkably stable and known to possess several biological functions such as microRNA sponging, regulating transcription and splicing and occasionally acting as polypeptide-producing templates. CircRNAs show tissue-specific expression and have been reported to be associated with the progression of several types of malignancies. Given the recent progress in genome sequencing and bioinformatics techniques, a rapid increment in the biological role of circRNAs has been observed. Concurrently, the patent search from different patent databases shows that the patent number of circRNA is increasing very quickly. These phenomena reveal a rapid development of the technological landscape. In the present review, the recent progress on circRNAs in various kinds of cancer has been investigated and their function as biomarkers or therapeutic targets and their technological landscape have been appreciated. A new insight into circRNAs structure and functional capabilities in cancer has been reviewed. Continually increasing knowledge on their critical role during cancer progression is projecting them as biomarkers or therapeutic targets for various kinds of cancer. Thus, recent updates on the functional role of circRNAs in terms of the technological landscape, clinical opportunities (biomarkers and therapeutic targets), and challenges in cancer have been illustrated.

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1. Introduction

Cancer accounts for more than 10 million mortalities and is the second most leading cause of death worldwide, and it is estimated that nearly 30 million patients will succumb due to cancer each year by 2040 (1). Cancer is a disease that can start occurring in any tissue of the body where cell growth is uncontrollable and starts spreading to other parts of the body, leading to metastasis, a major cause of death in patients with cancer. Inability to contain physiological apoptosis leads to cancer development and is a reason for resistance to radiotherapy and chemotherapy (2). Certain of the common types of cancer in women are cervical, breast, colorectal, thyroid

and lung, while men commonly have cancers such as prostate, colorectal, lungs, liver and stomach (3). At present, numerous treatments, including radiation, chemotherapeutic drugs and surgical operations, have been introduced to treat cancer, which often leads to the damage of healthy cells and enhances the toxicity in the patients. Thus, currently, researchers emphasize eliminating only cancerous cells without hampering the normal functioning of the body. Application of chemotherapy and radiotherapy are the primary major interruptions of most cancers, but due to the presence of acquired and intrinsic resistance, their therapeutic efficiencies have been retarded. Several limitations are making current therapies ineffective against cancer which includes, firstly, non-specific mechanisms of action, eliminating not only the cancer cells but also the normal cells; secondly, the metastatic ability of cancer cells to other tissues other than the primary cancer site, and lastly, non-availability of efficient diagnosis system due to lack of effective biomarkers (4). Hence, researchers nowadays are looking for more biochemically relevant alternatives to cancer cells that can be targeted for their reliable specificity and are participants in the regulatory mechanism of cancerous cells.

In previous studies, it has been found that circular RNAs (circRNAs) play a major role in tissue homeostasis and cellular differentiation, which even leads to the development of diseases (5,6). Previously, circRNAs were considered peculiarities having no specific biological functions and being a result of an error in the process of splicing (5). It has been found that there is often no correlation between linear expressions of host gene circRNAs. This leads to an understanding that circRNAs are not just a product of normal mRNA splicing but a product of alternative splicing, which is finely regulated (6). The circRNA sequence was analyzed, and it was found that they are conserved and have certain biological importance. Biological functions of circRNAs have recently become fascinating in the scientific world and the scientific community is very much curious to investigate it. Therefore, more therapeutic approaches are being developed by knowing the function of circRNAs, and their specific role in diseases has been revealed with the help of the advancement of science and technology. CircRNAs are non-coding RNAs present in the genome having different functions of regulating various molecules such as mRNAs, DNAs, non-coding RNAs and proteins to regulate cell functioning and physiology of an organism (7). Structures of circRNAs have a covalently closed circle. Regions of introns involved in circle formation are more likely to consist of inverted complementary Alu repeats, and these regions of Alu repeats act as transposons within the genome. With the help of base pairing between Alu repeats, circularization becomes markedly easier as it facilitates splice site recognition (8,9). CircRNAs are highly stable in the body due to their circular structure, which safeguards them from the effect of enzymes like exonucleases.

In the development of tumors, circRNAs play a vital role and enhance the effectiveness and sensitivity in chemotherapy and radiation (10). Several studies have shown that certain circRNAs are expressed abnormally in tumor cells, but it does not always promote the cause of malignancy; nevertheless, it takes part in the regulation of tumorigenesis (11,12). Multiple varieties of tumors, particularly those originating from the gastrointestinal tract and ovary, impart a stronger preference to the peritoneal cavity as the site of metastasis. A balance mediates the spread of malignancy in the intraperitoneal region between normal residential peritoneal cells and cancer cells that are actively invading (10). Numerous genes produce stable and conserved closed circRNA with a high potential for gene regulation (12). This knowledge may lead to targeting specific circRNA to cure different types of cancer. In the pathogenesis of human cancers such as lung, liver, ovarian, breast, prostate, including tumors and malignancies in the central nervous system, circRNAs are being found to play a crucial role in the development of cancers. CircRNAs are very much tissue-specific, having distinct expressions for different diseases and they are specific hallmarks of cancer (13,14). CircRNAs are detectable in fluids such as saliva and blood (15-18). Recent research is progressing rapidly in recent times on circRNAs after discovering this non-coding RNA in 1976 (Fig. 1). Furthermore, scientists are trying to discover the biological mechanisms behind cancer development regulated by circRNAs and assessing them as biomarkers, making the process of diagnosis easier and promoting personalized medicine.

Thus, in the present article the role of recently discovered circRNAs in cancer development has been illustrated and how they may offer therapeutic potential for the cure of cancer has been reviewed. Moreover, technological advances in the field of discovery and annotation of circRNAs, clinical relevance and manifestations, and commercial biopharmaceutical aspects (patents) have also been discussed elaborately.

2. Biogenesis of circRNA

In most eukaryotic genes, intronic sequences between the exons are removed by the spliceosome from the nascent precursor mRNA. As per the literature available, it has been considered for long that after transcription, most introns are removed sequentially and rapidly to allow exons to link to form a functional linear mRNA covalently. The well-regulated splicing process generates a diversity of functional spliced transcripts with distinctive exon arrangements (19). CircRNAs also undergo this splicing mechanism to form a covalently linked structure. Though information regarding the regulation of circRNA biogenesis is not very clear, it has the characteristic of covalently joining of 3' end of one exon to upstream of 5' end by the process of back splicing to form circRNA with the help of flanking Alu repeats in circularized exon (20-24). Back splicing can be regulated by binding splicing factors to regulatory elements of the cis-acting splicing site (25,26). An alternative process for circRNA biogenesis includes lariat precursors in exons which can be spliced internally, and introns can be removed to produce mature circRNA (27). Studies have shown that outcomes of back-splicing are related to the elongation rate of RNA Polymerase II and are under the tight control of cis-elements (28,29). Moreover, circRNAs are mainly processed posttranscriptionally and are stable. Strikingly, endogenously the productivity of circRNA from pre-mRNA is exceptionally low (28). Nevertheless, certain circRNAs are in higher concentration than their related linear mRNAs, particularly in the nervous system, and can play a substantial role in organismal phenotypes (29). A majority (>80%) of

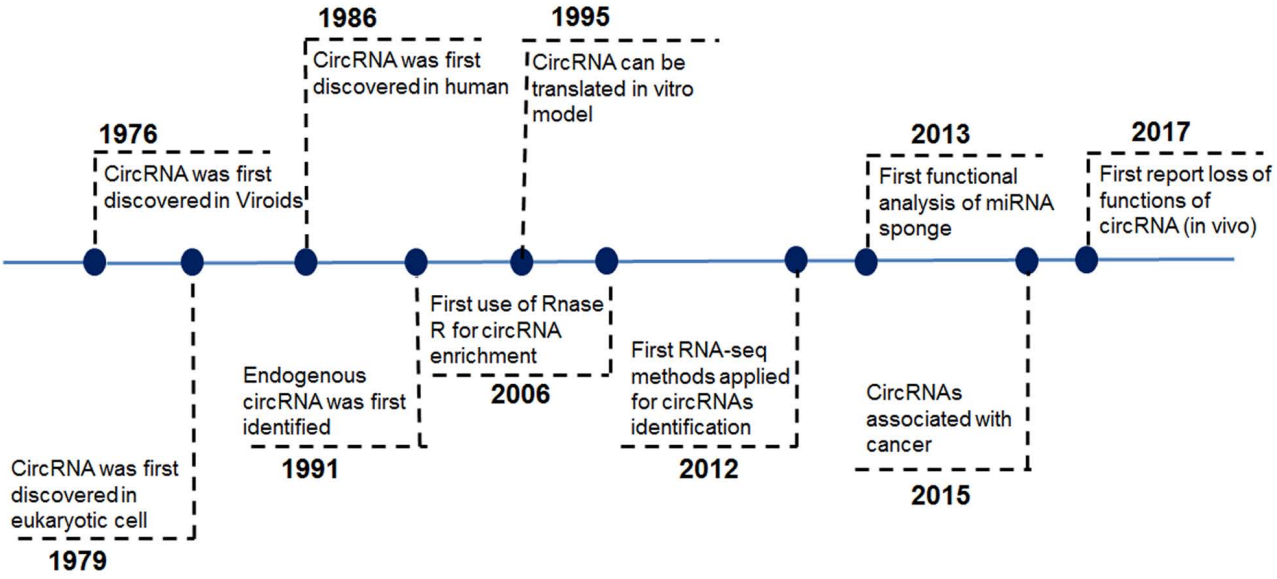

Figure 1. Timelines of different milestone discoveries of circRNA research (circRNA, circular RNA).

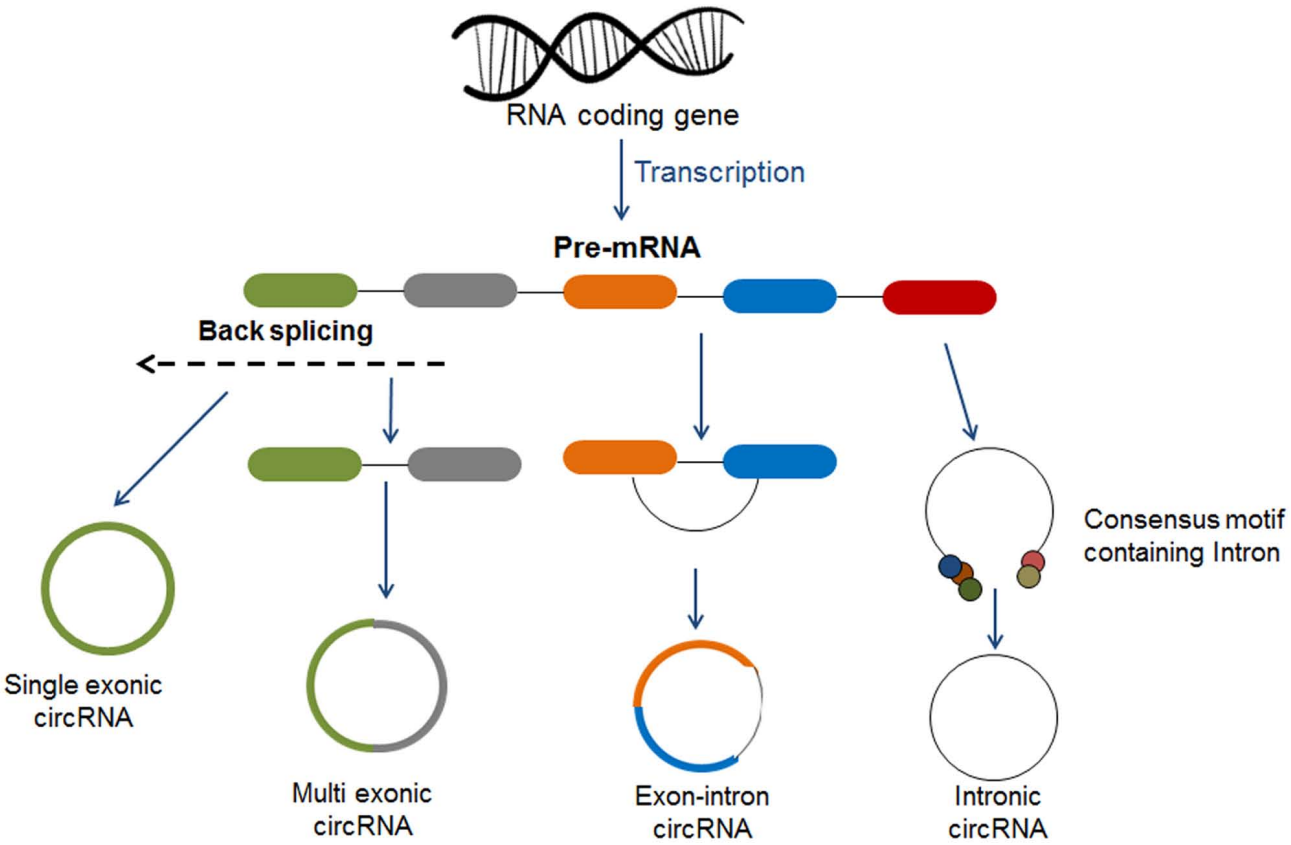

Figure 2. Different types of circRNA concerning the biogenesis model (circRNA, circular RNA).

circRNAs are derived either from single or several exons in humans and are termed exonic circRNAs (ecircRNAs). Other than ecircRNAs, high-throughput sequencing has identified three other types of circRNAs, which are exon-intron circular RNAs (EIciRNAs), having both introns and exons; circular intronic RNAs (ciRNAs), having introns only; and tRNA intronic circular RNAs (tricRNAs), makes stable circRNA via pretRNA splicing (Fig. 2) (19,30).

3. Length of circRNA

Previous studies showed that the length of circRNAs generally consists of 1-5 exons, and it has also been suggested that length of exons may be crucial in deciding whether the exon will circularize or not (6,31). The size of exons in circRNAs varies, and it can be three times longer as compared with the average exons that are expressed. Introns that are present adjacent to

the exons which get circularised are also three times longer as compared with introns that are not present in the flanking regions of pre-circle exons (31). During the process of circRNA formation, mostly exon 2 is considered as the acceptor exon, and it is present upstream (32).

4. Difficulty in detecting circRNA

The detection of circRNA is an arduous task as reverse-transcription quantitative PCR (RT-qPCR) assays are unable to differentiate between normal linear RNA and circRNA in the presence of a template of the linear genome for designing primers. The presence of poly-A tail makes rRNA purification easier, but circRNAs lack poly-A tail in them, thus it becomes even more challenging to detect them (33). In addition, detection issues such as high false discovery rate, underestimation of back-spliced junction reads, RNase R treatment efficiency, and uneven rRNA depletion further complicates the identification of circRNAs (34). Thus, various computational approaches having stronger algorithms (having efficient alignment-based strategies) are being employed for the characterizing of circRNAs.

5. Computational biology to identify circRNAs in cancer

Computational biology has immensely contributed to identifying the different novel circRNAs in cancer. Several scientists are developing various new bioinformatics tools and continuing their research in this direction (35,36). Multiple databases have been made available to researchers for circRNA analysis utilizing these developing techniques with continuing efforts. Certain bioinformatics tools are pcircRNA_finder (37), CircRNAFisher (38), find_circ, and circTools (39). These databases can be utilized to analyze various aspects of circRNAs, including anticipating probable interactions of circRNAs with desirable molecules, their ability to translate and make proteins, and evaluating any correlation with diseases. A comprehensive list of databases to identify the circRNA in various diseases, including cancer, has been listed in Table I. Though numerous circRNAs have been identified recently, limited information is available for their translation *in vivo* and probable biological functions.

6. Biological roles of circRNAs

Recent advances in high-throughput sequencing techniques and the development of various bioinformatics algorithms have facilitated the annotation and quantification process for circRNAs (40). Few studies have highlighted certain crucial functions of circRNAs, including protein sponges or decoys, microRNA (miRNA or miR) sponges, and DNA replication regulators.

CircRNA as protein sponges or decoys. There is a presence of multiple or single RNA binding protein sites within the circRNAs, which act as protein sponges. From the locus of mannose-binding lectin (MBL), the protein sponge of circRNA has been derived, which itself has the MBL protein binding site (21). MBL proteins can attach themselves with introns, flanking from circularized exons, and enhance their biogenesis process with autoregulation. It also leads to the prevention of MBL protein from binding to other potential targets when they are already bound with circRNAs. In the presence of excess MBL protein, their production can be regulated by forming circRNAs by decreasing their mRNA production. Human antigen R (HuR) binds to both mRNA of PABPN1 and circRNA from the gene *PABPN1* itself, and the translation process gets enhanced (17). Translation of HuR mRNA is controlled by binding of HuR to circPABPN1. mRNAs of several cancer-causing genes and tumor suppressor genes such as *BCL2, VHL, MYC, TP53* and *HIF1A* are the efficient targets for HuR. Information regarding the role of HuR directly in cancer remains unclear, and it needs to be investigated further (17,41). By modulating its expression of binding proteins through protein-protein interactions, circFOXO3 has been hypothesized to be involved in cancer (42). It was revealed that circFOXO3 could bind to p53 and MDM2 to sensitize the breast cancer cells to cisplatin and doxorubicin. Ubiquitination of p53 is also mediated by circFOXO3 and gradually gets degraded by the proteasome. More circRNAs that can function as protein scaffolds need to be detected to understand their molecular mechanisms in an improved way (43). At present, it can only be hypothesized that circRNA may form a complex with the proteins having tumor suppressor activity for preventing normal activities of the cells. However, to prove this hypothesis, further studies and analysis are required in the near future.

CircRNA as miRNA sponges or decoys. miRNA sponges or decoys depend upon the interaction between miRNAs and protein-coding RNAs or non-coding RNAs. Due to the predominant location of circRNAs in the cytoplasm, circRNAs may either compete for miRNA-binding sites to modulate the activity of miRNAs or act as competitive endogenous RNAs (44). circRNAs having the ability to regulate the activities of miRNAs have an indispensable role in the pathogenesis of cancers in humans (45,46). It was found that circRNAs have specific binding sites for miRNAs, and there is the absence of any single nucleotide polymorphism, which indicates the presence of conserved sequences within the organism (47). CircRNAs may contain multiple or single miRNA binding sites, and due to conserved sequences, miRNA regulation does not require multiple miRNA binding sites. However, circCCDC66 from the *CCDC66* gene provides more than one binding site for miRNAs, targeting oncogenes other than genes for tumor suppressors (48). mir-7 was the first circRNA sponge whose gene regulatory function was revealed, and it has 70 conserved sites for miR-7 binding and is present on the opposite strand of the *CDR1* gene, thus it is considered antisense CDR1 (6,44). Oncogenes are the target of miR-7, and its expression and stability were found to be higher in specific tissues of humans, as a result of which miR-7 targeting gene's expression will be increased by reducing the activity of miR-7 (49). CircRNAs possess the property of miRNA sponges along with their other molecular functions in the biological system (50). CircRNA, circRNAHIPK3, functions as the miRNA sponge for cancer, and binding sites for miRNA are being predicted and verified from the data derived from Argonaute HITS-CLIP of circRNA (51). Similarly, circPVT1

Table I. Different databases and webservers for detection and characterization circRNAs.

Sl. no.	Name of the databases	Year	Web links	Remarks
1.	circBase	2014	http://www.circb ase.org/	The server used for multiple information for a definite circRNA (genome location, tissue or cell line source and references) also available.
2.	circlncRNAnet	2018	http://app.cgu.edu.tw/circl nc/	The online analysis database which assimilates the circRNA and lncRNA functional network and supports for online visual analysis.
3.	deepBase v2.0	2016	http://deepb ase.sysu.edu.cn/	Webserver used for analysing and predicting the expression patterns, evolution, and functions of lncRNA in diverse species group.
4.	CircNet	2016	http://circn et.mbc.nctu.edu.tw/	It provides tissue specific expression of circRNAs and circRNA-miRNA-mRNA regulatory networks.
5.	TSCD	2017	http://gb.whu.edu.cn/TSCD/	Used for tissue-specific circRNAs evidence in humans and mouse model, also predicting bound miRNAs.
6.	circRNABase	2013	http://starb ase.sysu.edu.cn/ starb ase2/mirCi rcRNA .php	Creating the interaction networks of circRNA and miRNA, circRNA and RBPs.
7.	CSCD	2018	http://gb.whu.edu.cn/CSCD/	Servers used for tumor-specific circRNAs, predicting RBP binding sites, ORF, and analyzing the alternative splicing sites of related genes.
8.	CIRCpedia	2016	http://www.picb.ac.cn/rnomi cs/circp edia/	Used for the interpretations of back splicing events and alternative splicing mechanism for circRNAs from different cell lines or tissue parts.
9.	CircR2Disease	2018	http://bioin fo.snnu.edu.cn/ CircR 2Dise ase/	Revealing the relationship between circRNA and disease, and building an interaction network of circRNA and diseases.
10.	Circ2Traits	2013	http://gyanx et-beta.com/ circd b/	First database used for collection of circRNAs having potential association with the human disease or traits.
11.	circRNA disease	2018	http://cgga.org.cn:9091/ circR NADisease/	The database collect human disease-related circRNAs and examining by the disease name or circRNA name.
12.	exoRBase	2017	http://www.exorb ase.org/	This web server comprising lncRNA, mRNA, and circRNA, from serum exosomal RNA-seq sequencing samples.
13.	CircRNADb	2016	http://202.195.183.4:8000/ circr nadb/circR NADb.php	This circRNA database able to encode proteins, and provide information about the translational potential of circRNA and its linked proteins.
14.	CircInteractome	2016	https://circi ntera ctome . nia.nih.gov/	Predicts the potential binding sites for circRNA, miRNAs RBPs and circRNA, for designing nucleotide primers, siRNA for circRNAs
15.	MiOncoCirc	2015	https://mioncocirc.github.io/	The first extensive clinical, cancer-centric samples resource of circRNAs.

circRNA, circular RNA; lncRNA, long non-coding RNA; miR or miRNA; microRNA; RBP, RNA binding protein.

was found responsible for stimulating the growth of cells by sponging miR-125 family members (52,53). Another example is circRNA itchy E3 ubiquitin-protein ligase (circ-ITCH), which acts as a miRNA sponge to suppress tumor growth and increases the level of ITCH (54). It has been observed that the formation of miRNA and circRNA complex will not result in miRNA suppression, and circRNAs with binding sites for miRNA will function as the potential reservoir for miRNAs

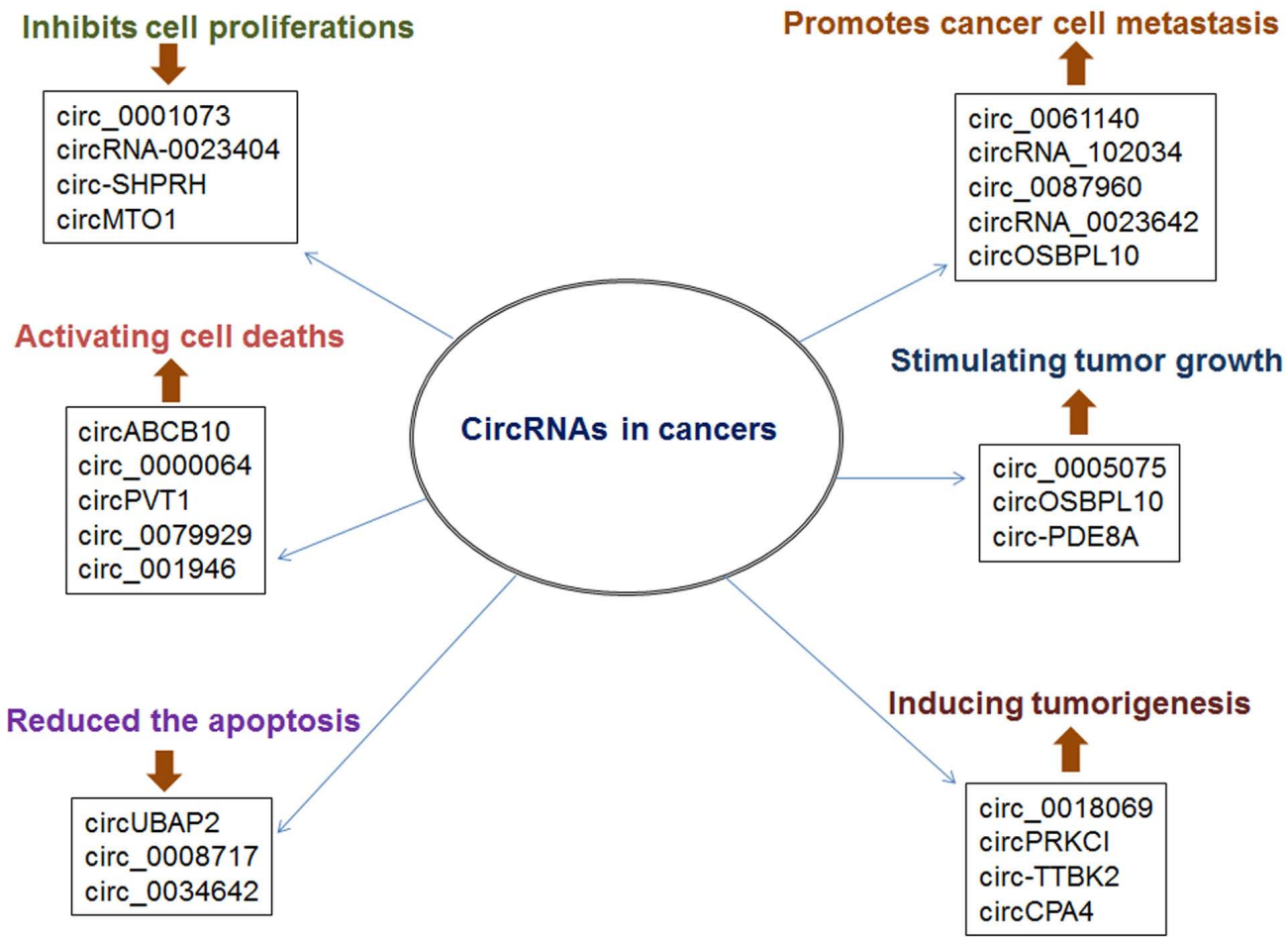

Figure 3. Multiple circRNAs are linked with different cancer mechanisms (circRNA, circular RNA).

and facilitate the transportation of miRNA to exhibit other molecular functions.

Regulation of splicing and transcription by circRNA. CircRNAs present in the nucleus can interfere in the transcription process or help initiate alternative splicing. Still, primarily circRNAs are present in the cytoplasm, where they may act as protein or miRNA decoys, scaffolds, or transporters. There is an association between RNA pol II and intron-exon circular RNA and U1 snRNP to enhance parental gene transcription (55). The formation of circRNA and functional mRNA are generally incompatible due to competition among linear and circular splicing of most of the genes from the host. Thus, a deviation in the balance between linear and circular splicing will lead to divergence in the normal transcription process of genes related to oncogenes or tumor-suppressor. ci-Ankyrin Repeat Domain 52 (ci-ANKRD52), an abundant RNA, stimulates transcription of its parental gene, *ANKRD52*, by interacting with the elongation pol II complex and getting accumulated at the transcription sites (56). It has been reported that a special class of circRNAs, EIciRNA-U1 (small nuclear ribonucleoprotein (snRNP) complexes amid U1 snRNP and EIciRNAs), may interact with factors like U1 snRNP through RNA-RNA interaction. To stimulate gene expression of its parental genes, EIciRNAs-U1 snRNP complexes may further interact with the RNA pol II transcription complex at the promoter site (55).

7. Role of circRNAs in cancer

Previous studies suggested circRNA as the prominent hallmarks of cancer (48,51). In the present review, certain of the circRNAs and their potential functional role in the regulation of cancer will be discussed (Fig. 3). Still, circRNAs are involved in various diseases in humans apart from cancer. Researchers are trying to explore the fundamental molecular mechanisms behind the process of overexpression or knockdown of specific circRNAs and their effect on cell cycle progression and to regulate different significant proteins (Fig. 4). CircRNA found from the *Foxo3* tumor suppressor gene has the potential to cause apoptosis of cancer cells (18,42). Circular Foxo3 may interact with MDM2 and p53 to indirectly upregulate the linear host gene. The interaction between Foxo3 and MDM2 can be decreased by overexpression of circular Foxo3, which leads to the release of Foxo3 from MDM2. In turn, the activity of Foxo3 is increased, causing Bax and Puma-mediated apoptosis (42). Inhibition of progress in the cell cycle and angiogenesis is also modulated by Foxo3 circRNA. The formation of the ternary complex, including circular Foxo3-p21-CDK2, inhibits CDK2 to promote cell cycle progression (42,57). Circular ZFN292 induced by hypoxia also has the properties of tumor suppression and negative regulation of cell cycle progression, and it also shows proangiogenic functions (58,59). CircRNA from genes *UBAP2* and *TTBK2* possess the ability to inhibit apoptosis (28,60). No scientific evidence has

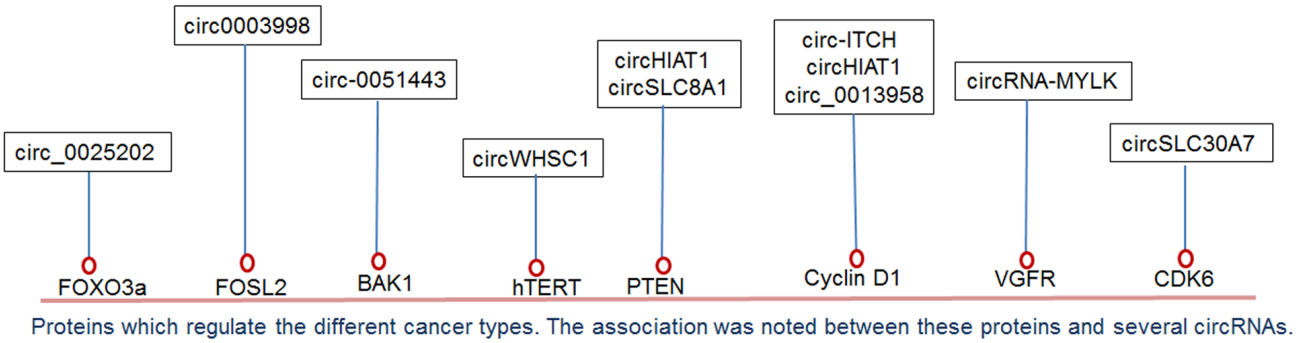

Figure 4. Different proteins that are associated with circRNAs and regulate various cancers (circRNA, circular RNA).

been found that circular ZFN292 functions as a miRNA sponge, and there is no data to show the binding of argonaute protein to circular ZFN292. Another evidence of promoting angiogenesis by circRNA-MYLK is mediated via the signaling pathway of vascular endothelial growth factor (61). Circular TCH is another circRNA that inhibits the β-catenin pathway and negatively regulates the cell cycle (62,63). Cell cycle proliferation gets reduced by the activity of circMTO1 by dissociating p21 and miR-9 complex and leads to downregulation of cell cycle (64).

By contrast, circRNA-7 positively affects cell cycle progression by inhibiting miR-7 activity and enhancing the mitogen-activated protein kinase pathway (65). On the other hand, the expression of cyclin-dependent kinase 6 (CDK6) is increased by circSLC30A7, which leads to the enhancement of cell cycle progression (66). The effect of circRNAs like circCCDC66, circZKSCAN1, circHIAT1 and circKCNH1 in metastasis has been identified *in vivo* and *in vitro* studies (62,63,66,67). Numerous circRNA expressions usually deviate from their normal functioning in the initial cancer stage but are even detectable at the later stages of diagnosis (63,68).

8. Significance of circRNAs in cancer

It is evident from previous studies that specific circRNAs are being translated in certain tissues under particular conditions only (69,70). It has been observed that different types of human cancer have been regulated by several circRNAs (Table II). Currently, the circRNA translation procedure *in vivo* is not well known. Still, there is evidence of the presence of elements like ribosomal entry sites and AUG sites within the circRNAs (31). The functioning of circRNAs is not dependent upon their host gene, and instead, they are regulated independently. For detecting and mapping miRNA binding sites and RNA binding proteins on human circRNA, a new web tool has been established named CircInteractome to make understanding more accessible and quicken analysis (157). Another database named MiOncoCirc has been made available for the progress of circRNAs as diagnostic or therapeutic candidates in various types of cancer (158).

9. Early cancer detection using next-generation circRNA-based biomarkers

Detection of cancer at the initial stages remains a challenge in the fight against cancer. A scarcity of reliable biomarkers has always been a hindrance in this cause. Early diagnosis of cancer and treatment at the initial stages can save the life of the patient. Thus, the advances in next-generation biomarkers are an urgent prerequisite to address this issue (159). Next-generation biomarkers could help to detect diseases very quickly and efficiently. To diagnose cancer at an early stage, scientists are trying to develop the next-generation biomarkers. Specifically, circRNAs are emerging as reliable biomarkers for detecting different types of cancer (160,161). Several circRNAs-based biomarker development incentives are listed in Table III. However, more studies are required to develop the next-generation circRNAs-based biomarker.

10. Tissue-specific functions of circRNAs in different cancers

circRNAs in hematological malignancies. With the help of the RNA-seq analysis approach, it has been found that the expression of circRNAs varies from different tissues and at various stages of development (173). Platelets are translationally competent circulating blood cells with a significant circRNA reservoir. Though several circRNAs have been reported from cultured platelets, the number of circRNAs in cultured cells is quite smaller than in matured platelets (71,174,175). Hence, further research is required in platelets derived from patient samples to understand the role of circRNAs. Another aspect is the circRNAs present in the vesicles (exosomes and microvesicles) which are generated from platelets. An abundant amount of circRNAs are present in exosomes compared with platelets. By varying the miRNAs associated with the sorting and loading of circRNAs into exosomes, circRNAs may be made to transfer in recipient cells as required. Nearly ~1,000 circRNAs have been reported from serum exosomes of patients with colon cancer. Identified circRNAs may be utilized to distinguish between patients with colon cancer and healthy normal individuals (14). In KRAS mutant colon cancer cells, ample circRNAs were observed in secreted extracellular vesicles and then exosomes compared with cells (176). From 170 patients and 45 healthy controls, a RT-qPCR analysis of circulatory exosomes revealed that hsa_circ_0004771 could be used to differentiate patients with CRC stage I/II and benign intestinal diseases (177). In liver-metastatic pancreatic ductal adenocarcinoma (PDAC) tissues, a high expression of circPDE8A was reported and was shown to be closely related to lymphatic infiltration, TNM stage, and tumor status. Further

Table II. Role of circRNAs in different types of human cancer.

Type of cancer	CircRNA	Type of sample	Regulation in tumour	Function	Mechanism	(Refs.)
BC	circABCB10	Tissue	Upregulation	Oncogene	Increases BC cell apoptosis and decreases proliferation.	(71)
	circ_0005505	Cells	Upregulation	Oncogene	Promotes cell migration, invasion and metastasis without affecting cell proliferation, colony formation or cell cycle progression.	(72)
	circ_0001982	Tissue	Upregulation	Oncogene	Progression of breast cancer tumorigenesis by cellular proliferation and invasion.	(73)
	circ_0141206	Cells	Downregulation	Tumour suppressor	Suppresses the BC stem cells expansion and self-renewal capability.	(74)
	circ_0000911	Tissue	Downregulation	Anti-oncogenic	Cellular proliferation increase, sponge to miR-449a.	(75)
	circ_0008039	Tissue	Upregulation	Oncogene	Suppresses cellular proliferation, arrests cell-cycle progression and reduces migration of cells in breast cancer.	(76)
	circ_0006528	Cells	Upregulation	Oncogene	Having chemo resistance properties targeted to miRNAs sponges.	(77)
	circ_0008717	Cells	Upregulation	Oncogene	Increases the cellular proliferation and reduces he apoptosis of breast cancer cells.	(78)
	circ_0007294	Tissue	Upregulation	Oncogene	Closely linked with lymph node metastasis and serves as an independent risk factor for invasion of BC cells.	(79)
	circ_0006220	Cells	Downregulation	Anti-oncogenic	Directly associated with the increased lymphatic metastasis and advanced clinical stage.	(80)
	circDENND4C	Cells	Upregulation	Oncogene	Hypoxic conditions influence proliferation of BC but knockdown of 1α inducible factor will decrease the BC proliferation.	(52)
	circ_0001358	Cells	Upregulation	Oncogene	Linked with miRNAs to elevated the cancer cell progression.	(81)
	circ_0025202	Tissue	Downregulation	Tumour suppressor	It suppresses cell tumorigenesis and tamoxifen resistance with miRNAs.	(82)
	circSMARCA5	Tissue	Downregulation	Tumour suppressor	Induced the drug sensitivity of breast cancer cell lines *in vivo* and *in vitro* model.	(83)

Table II. Continued.

Type of cancer	CircRNA	Type of sample	Regulation in tumour	Function	Mechanism	(Refs.)
LC	circ_0000064	Tissue	Upregulation	Oncogene	Causes apoptosis by silencing circRNA which stops progression of cell cycle.	(19)
	circRNA_102231	Tissue	Upregulation	Oncogene	Upregulates the lung adenocarcinoma with high expression in lymph node metastasis.	(84)
	circPVT1	Cells	Upregulation	Oncogene	Promotes tumergenesis, cell growth and invasion in a miRNA-dependent manner.	(85)
	circ_0013958	Tissue	Upregulation	Oncogene	Performs as sponge of miR-134, and upregulates the oncogenic cyclin D1 leading to LC.	(68)
	circPRKCI	Tissue	Upregulation	Oncogene	It functions as a sponge for miR-545 and miR-589 and promotes the tumorigenesis of lung adenocarcinoma.	(86)
	circ_0001649	Tissue and cells	Downregulation	Tumour suppressor	It inhibits cell growth and metastasis by miRNA sponges.	(87)
	circ_0007874	Cells	Downregulation	Tumour suppressor	Negative regulator of lung adenocarcinoma by directly interacting with miR-7 and miR-124.	(88)
	circRNA-FOXO3	Tissue	Downregulation	Tumour suppressor	Enhances LC cell migration and proliferation.	(89)
	circARHGAP10	Tissue	Upregulation	Oncogene	It acts as a sponge of the antioncogene and promotes the progression of LC.	(90)
	circRNA_100876	Tissue	Upregulation	Oncogene	Elevates the carcinogenesis of non small cell LC.	(91)
HCC	circMTO1	Tissue	Downregulation	Tumour suppressor	Expression enhancement of p21 to decreasing HCC proliferation.	(78)
	circRNA_102034	Tissue	Upregulation	Oncogene	Its expression profile significant upregulates the HCC by proliferation and metastasis.	(92)
	circZKSCAN1	Tissue	Downregulation	Tumour suppressor	Blocks proliferation of cells and helps in cancer signalling.	(93)
	circ0003998	Tissue	Upregulation	Oncogene	Upregulated in the nucleus and cytoplasm of the cell to prompte metastasis.	(94)
	circ_0005075	Tissue	Upregulation	Oncogene	Helps in tumor progression proliferation, invasion and metastasis.	(95)
	circ_0051443	Tissue	Downregulation	Tumour suppressor	It supresses the tumor microenvironment by acting as cell-cell mediator.	(96)
	circ_0079929	Cell	Downregulation	Tumour suppressor	Tumor suppressive role and helps in apoptosis.	(97)

Table II. Continued.

Type of cancer	CircRNA	Type of sample	Regulation in tumour	Function	Mechanism	(Refs.)
	circ_0091579	Tissue	Upregulation	Oncogene	Significantly upregulated via the regulation of miR-431.	(98)
	CircRNA GFRA1	Tissue	Upregulation	Oncogene	Expression promotes to the growth and invasion of HCC.	(99)
	circC3P1	Tissue	Downregulation	Tumour suppressor	Expression stimulation of phosphoenolpyruvate carboxykinase 1 in HCC cells by miR-4641 sponging.	(100)
OS	circPVT1	Tissue	Upregulation	Tumour promoter	ABCB1 expression decreases by circPVT1 knockdown.	(101)
	circ_0001258	Tissue	Upregulation	Oncogene	Interacts with miRNA sponge of miR-744 and chemo-resistant to cell proliferation.	(102)
	circUBAP2	Tissue	Upregulation	Oncogene	Progression of cancer cells as miRNAs sponge.	
	circ_0016347	Tissue	Upregulation	Oncogene	Performed as a positive regulator in OS cells proliferation and invasion with sponge of miR-214.	(63)
	circ_0001564	Tissue	Upregulation	Tumour promoter	Acts as miR-29c-3p sponge to mediate the tumorigenicity, promotes proliferation activity.	(104)
	CircLRP6	Tissue	Upregulation	Oncogene	Binds with the LSD1 and EZH2 to inhibit expression of KLF2 and APC protein.	(105)
	circ_0009910	Cells	Upregulation	Oncogene	MiRNA sponge with miR-449a to induce cell proliferation and growth.	(106)
Gliomas	circ-TTBK2	Tissue	Upregulation	Oncogene	Tumorigenesis suppression by acting as sponge for miR-127.	(63)
	circ-FBXW7	Tissue	Downregulation	Tumour suppressor	It inhibits the cellular proliferation and cell cycle acceleration in cancer cells.	(107)
	cric-FBXW7	Tissue	Downregulation	Tumour suppressor	Positively effects in survival of glioblastoma patients.	(62)
	circSCAF11	Tissue	Upregulation	Oncogene	It positively regulates the SP1 expression by sponging miR-421.	(108)
	circ_0034642	Cells and tissue	Upregulation	Oncogene	Regulation on miR-1205/BATF3 pathway and promotes cell growth, migration and invasion and inhibit cell apoptosis.	(109)
	circ_001946	Cells	Downregulation	Tumour suppressor	Combined effect with miR-671-5p reduces proliferation, migration, and invasion and increases apoptosis in glioma cells	(110)
	hsa_circ_ 0000177	Cells	Upregulation	Oncogene	It activates Wnt signaling and facilitates glioma growth.	(111)
	circ_0074362	Cells and tissue	Upregulation	Oncogene	Acts as sponge of miR-1236-3p to promote HOXB7 expression, increases cell proliferation, migration, and invasion.	(112)
Ovarian cancer	CircPLEKHM3	Tissue	Downregulation	Tumour suppressor	Its blocks the tumor promoting factors by targeting the miR-9/BRCA1/ DNAJB6/KLF4/AKT1 axis.	(113)
	hsa_circ_ 0061140	Tissue	Upregulation	Oncogene	It sponges with miR-370 and promotes cancer cell metastasis and cell growth.	(114)

Table II. Continued.

Type of cancer	CircRNA	Type of sample	Regulation in tumour	Function	Mechanism	(Refs.)
	circWHSC1	Tissue	Upregulation	Oncogene	Specific with sponging miR-1182 and miR-145 that upregulate the downstream targets expression of hTERT and MUC1.	(115)
Colorectal cancer	circ_001569	Tissue	Upregulation	Oncogene	miR-145 upregulation and targets BCL2 and E2F5.	(116)
	circ_101555	Tissue	Upregulation	Oncogene	Combined with miR-597-5p to upregulate RPA3 and CDK6 gene. expression in regulating colon cancer cell	(117)
	circCCDC66	Tissue	Upregulation	Oncogene	Oncogenic functions in cancer progression and metastasis.	(48)
	circ_0001313	Cells	Upregulation	Oncogene	Sponges with miR-510-5p, thereby upregulating AKT2.	(118)
	hsa_circ_0000069	Tissue	Upregulation	Oncogene	Acts as important regulator in cancer progression.	(119)
	hsa_circ_001988	Tissue	Upregulation	Oncogene	It has an insightful role in differentiation and perineual invasion of cancer tissues.	(120)
	circ_0140388	Tissue	Upregulation	Oncogene	Its acts cancer promoting effects in colorectal cancer by sponging miR-486	(121)
	circ_0001900	Tissue	Upregulation	Oncogene	Performs as a sponge of miR-328-5p, and stop its suppression on E2F1 transcription factor.	(122)
	circ-BANP	Tissue	Upregulation	Oncogene	Overexpresses for proliferation of cancer tissues.	(123)
	cir-ITCH	Tissue	Downregulation	Tumour suppressor	ITCH enhancement by cir-ITCH to repress Wnt/b-catenin.	(124)
LAC	hsa_circ_0013958	Tissue	Upregulation	Oncogene	Upregulation of cyclin D1 and acts as miR-134 sponge and enhances cell proliferation.	(125)
	circRNA_102231	Tissue	Upregulation	Oncogene	Enhances cell proliferation and reduces survivability of patients with LAC.	(107)
Cervical cancer	circRNA-0023404	Tissue	Upregulation	Oncogene	Decreases cell proliferation by knocking down of circRNA-0023404.	(126)
	circRNA-000284	Cells	Upregulation	Oncogene	Activity of miR-506 gets inhibited by binding to it and cell proliferation stops by circRNA-000284 knockdown.	(127)
Bladder cancer	circTCF25	Tissue	Upregulation	Oncogene	Enhances expression of CDK6 and increases cell proliferation.	(68)
	CircBCRC3	Tissue	Downregulation	Tumour suppressor	It binds with miR-182-5p/p27 axis and inhibits the cancer cell proliferation.	(128)
	circ_0001073	Tissue	Downregulation	Tumour suppressor gene	Stops the cancer cell proliferation and metastasis through miR-626/ EYA4 axis.	(129)

Table II. Continued.

Type of cancer	CircRNA	Type of sample	Regulation in tumour	Function	Mechanism	(Refs.)
	circ_0000285	Tissue	Downregulation	Tumour suppressor gene	Shows lower expression profile in cisplatin-resistant bladder cancer.	(130)
	circMTO1	Tissue	Downregulation	Tumour suppressor gene	It sponges with miR-221 and negatively regulates the E-cadherin/N-cadherin pathway to inhibit cancer cells.	(90)
	circ_0018069	Tissue	Upregulation	Oncogene	It helps in tumorigenesis by the adhesion signaling pathway of different miRNAs.	(131)
	circRNA-3	Tissues and cells	Downregulation	Tumour suppressor gene	Combined with miR-182-5p/p27 axis to supress the bladder cancer cell proliferation.	(128)
	circ-ITCH	Tissue	Downregulation	Tumour suppressor gene	Helps in the regulation of tumour suppression.	(84)
	circSLC8A1	Cells	Downregulation	Tumour suppressor gene	It complies with miR-130b, miR-494/ PTEN axis and suppresses the progression of bladder cancer cells.	(132)
	circPRMT5		Upregulation	Oncogene	This circRNA sponges miR-30c and supports the cancer signaling pathway for bladder cancer cells.	(133)
	circFNTA	Tissue	Upregulation	Oncogene	It sponges miR-370-3p to enhance the cancer cells progression.	(134)
	circ_0087960	Tissue	Upregulation	Oncogene	It links with the metastasis and invasion by miR-762.	(135)
	circRNA-MYLK	Tissue	Upregulation	Oncogene	Binds with miR-29a to activate the cancer signaling pathway of VEGFA/VEGFR2.	(61)
GC	circ_0047905	Cells	Upregulation	Oncogene	Promotes tumorigenesis and enhances GC pathogenesis.	(136)
	circ_0027599	Tissue	Downregulation	Tumour suppression	Its sponges miR-101 and suppresses the cancer cell survival and metastasis.	(137)
	circ_0000993	Cells	Downregulation	Tumour suppression	Its stops the invasion, migration and proliferation of cancer cells and performs as a miRNA sponge for miR-214-5p.	(138)
	circ_0017639	Tissue	Upregulation	Oncogene	Promotes cancel cells proliferation sponging with miR-182-5p.	(139)
	circ-DONSON	Tissue	Upregulation	Oncogene	Complex with the Nucleosome Remodeling Factor to elevate the cancer cells progression.	(140)
	circ_002059	Tissue	Downregulation	Tumour suppression	Supresses the malignant tumors and distal metastasis.	(141)
	ciRS-7	Tissue	Upregulation	Oncogene	It inhibits the miR-7-induced tumor suppression in cancer cells and leads to further proliferation.	(142)
	circNRIP1	Tissue	Upregulation	Oncogene	It sponges miR-149-5p to regulate expression level of AKT1 and ultimately performs as a tumour promoter.	(143)
	circ_0001461	Tissue	Downregulation	Tumour suppression	Interacts with YBX1 protein that inhibits GC cell proliferation,	(144)

Table II. Continued.

Type of cancer	CircRNA	Type of sample	Regulation in tumour	Function	Mechanism	(Refs.)
					migration and invasion.	
	circPSMC3	Tissue	Downregulation	Tumour suppression	It sponges miR-296-5p and suppresses the tumorigenesis of cancer cells.	(145)
	circYAP1	Tissue	Downregulation	Tumour suppression	It targets the miR-367-5p/p27 Kip1 axis to stop the cancer cell progression.	(146)
	circ_0000096	Tissue	Upregulation	Oncogene	It promotes the cancer cell growth and migration by interfering with the cyclin proteins.	(67)
	circRNA_0023642	Tissue	Upregulation	Oncogene	It acts as metastasis activator by promoting epithelial-mesenchymal transition-related proteins.	(147)
	circLARP4	Tissue	Downregulation	Tumour suppression	Stops the invasion and proliferation of cancer cells by sponging miR-424-5p and regulating LATS1 expression.	(148)
	circDLST	Tissue	Upregulation	Oncogene	Sponges miR-502-5p to stimulate the NRAS/MEK1/ERK1/2 cancer signaling pathway.	(149)
	circ_0049027	Tissue	Downregulation	Tumour suppression	Interacts with the CNBP protein and inhibits the cancer cells progression.	(150)
	circOSBPL10	Tissue	Upregulation	Oncogene	It promotes the cellular metastasis and tumor growth by circOSBPL10-miR-136-5p-WNT2 axis.	(151)
	circ_0000745	Tissue	Downregulation	Tumour suppression	Directly correlated with the tumor size and lymphatic metastasis.	(152)
	circ_0000520	Tissue	Downregulation	Tumour suppression	Interacts with mRNA-miRNAs and negatively regulates the progression of cancer cells.	(153)
	hsa_circ_0138960	Tissue	Upregulation	Oncogene	Regulates the expression of parental gene to malignancy development and progression of cancer cells.	(154)
	has-circ RNA7690-15	Tissue	Upregulation	Oncogene		
	hsa_circ_0047905	Tissue	Upregulation	Oncogene		
	circRNA_101057	Cells	Downregulation	Tumour suppression	Prevents cellular invasion and proliferation to stop lymphatic metastasis, affecting miR-424.	(148)
Cholangio carcinoma	circ_0001649	Tissue	Downregulation	Tumour suppression	Reduces proliferation of cells and enhances cell apoptosis.	(155)
	circ-CCAC1	Cells	Upregulation	Oncogene	It sponges miR-514a-5p to upregulate the angiogenesis of cancer cells.	(156)

hsa, *Homo sapiens*; BC, breast cancer; LC, lung cancer; circRNA, circular RNA; miR, microRNA; HCC, hepatocellular carcinoma; OS, osteosarcoma; GC, gastric cancer; LAC, lung adenocarcinoma.

Table III. CircRNAs as next-generation novel biomarkers for different cancers.

Sl. No.	Types of cancer	Name of the circRNA used as biomarker	Remark	(Refs.)
1.	Gastric cancer	hsa_circ_0000190	This circRNA is downregulated in gastric cancer plasma samples and tissue samples.	(162)
		hsa_circ_0000520	It is downregulated in tissues and plasma in gastric cancer.	(153)
		hsa_circ_0002874	It was detected from the peripheral blood of patients, which may show a diagnostic value.	(163)
2.	HCC	hsa_circ_0001649	The patient sample showed that the circRNA was significantly downregulated in HCC tissues.	(164)
		SMARCA5	It was detected from the plasma sample with a high level of accuracy.	(165)
3	CRC	hsa_circ_0001649	It is downregulated in CRC.	(166)
		ciRS-7	It has been noted that circRNA was significantly upregulated in CRC tissues.	(64)
4	Lung adenocarcinoma	hsa_circ_0013958	It can be used as a potential biomarker early detection of the potential non-invasive biomarker for the early screening detection and detection of lung adenocarcinoma.	(158)
		hsa_circ_0000729	42 tissue samples shows that this circRNAcan be a potential biomarker of lung adenocarcinoma.	(167)
5.	Ovarian cancer	hsa_circN4BP2L2 and hsa_circEXOC6B	It has been noted that it can be a novel biomarker of ovarian cancer (observed from the 54 epithelial ovarian cancer samples).	(168)
6.	Thyroid cancer	hsa_circ_0006156	It can be a novel biomarker of thyroid cancer which was noted to be upregulated in serum samples of patients with papillary thyroid cancer.	(169)
7.	Non-small cell lung cancer	hsa_circ_0014130	It is a potential biomarker of non-small cell lung cancer which was detected through a microarray profile.	(170)
8.	Breast cancer	hsa_circ_0001785	This circulating circRNA can be a potential biomarker for breast cancer detected in the plasma sample of patients with breast cancer.	(171)
9.	Cervical cancer	hsa_circYPEL2	This circulating circRNA can be a potential biomarker for cervical cancer, which is highly expressed in patients with cervical cancer.	(172)

hsa, *Homo sapiens*; HCC, hepatocellular carcinoma; CRC, colorectal cancer; circRNA, circular RNA.

studies on the plasma of PDAC patients further confirmed that the tumor cells release exosomes with circPDE8A (178).

In patients with acute myeloid leukemia (AML), hsa_circ_0009910 is overexpressed in the bone marrow. It was found to sponge miR-20a-5p and associated with poor overall survival of patients. Eliminating hsa_circ_0009910 resulted in the induction of apoptosis in AML cells (179). On the other hand, expression of hsa_circ_0004277 was found to be downregulated in patients with AML. Expression of hsa_circ_0004277 appeared to be restored after chemotherapy and thus can be considered a potential therapeutic target for AML (180). In patients with AML, circRNA, circMYBL2, is overexpressed, having FLT3-ITD mutations. Knockdown of circMYBL2 inhibits growth and promotes differentiation of FLT3-ITD AML (181). In the case of chronic myeloid leukemia (CML), overexpression of hsa_circ_0009910 sponges miR-34a-5p to induce imatinib resistance. Elimination of hsa_circ_0009910 decreases imatinib resistance and inhibits cell growth by inducing autophagy and apoptosis (182). In chronic lymphocytic leukemia (CLL), upregulated circRPL15 sponges miR-146b-3p to activate the RAS/RAF1/MEK/ERK signaling pathway axis and induce the development of CLL (183).

Human peripheral whole blood contains a substantial amount of circRNAs, which may project them as diagnostic tools for cancer. In human peripheral blood mononuclear cells (PBMCs), a comprehensive and abundant expression

of circRNAs has been observed. It was observed that the expression of circRNAs in PBMCs of patients with active tuberculosis was different than in healthy controls (184). Another analysis revealed that five circRNAs were increased in the blood of patients with coronary artery disease (CAD) compared with control (healthy individuals) (185). Among these five circular miRNAs, the highly expressed was hsa_circ_0124644. A study on plasma circRNAs to diagnose patients with hepatocellular carcinoma (HCC) with hepatitis B virus (HBV) observed that hsa_circ_0007750, hsa_circ_0000976 and hsa_circ_0139897 were significantly higher in patients with HCC than in patients with HBV-related liver cirrhosis and in healthy controls (186). The circ-STIL, circ-ABCC1, and circ-CCDC66 in the plasma of patients with colorectal cancer (CRC) were substantially decreased than in the control group. For CRC diagnosis, together, these three circRNAs demonstrated a specificity of 85.2% and sensitivity of 64% (187). It was noted from the aforementioned study that f-circRNAs (from fusion genes) have unique characteristics as tumor biomarkers due to their highly cancer-specific expression.

Breast cancer (BC). BC remains one of the primary causes of cancer-related deaths in women worldwide (1.7 million breast cancer cases and 521,900 breast cancer-related deaths were reported in 2012) (188). Several treatments such as hormone therapy, targeted therapy and chemotherapy are being implemented to cure one of the most expensive malignancies such as breast cancer. ~1/5 of breast cancers worldwide are diagnosed as ductal carcinoma *in situ* (DCIS) (189). Though it is treatable, it becomes a life-threatening type as invasive ductal cancer (IDC) in a few cases. The hsa_circ_0122662 and hsa_circ_0001358A were found in the screening of the circRNAs in five patients with DCIS/IDC and MCF-7 (breast cancer cell line) (189). From the Starbase human pan-cancer tool it was established that hsa_circ_0001358 was related to five miRNAs (miR-376a-3p, miR-200c-3p, miR-429, miR-376b-3p and miR-200b-3p). Since a differential surge in the dynamic expression of circRNAs was observed in DCIS or IDC, more future studies are prerequisites to explore the function of these circRNAs in breast cancer prognosis.

A high-throughput circRNA microarray from samples of patients with triple-negative breast cancer (TNBC) revealed that circEPSTI1 (*EPSTI1* gene) was a highly expressed circRNA among the overexpressed circRNAs in the majority of TNBC cells and tissues, and its deletion induced apoptosis and suppressed cell proliferation. Additionally, increased expression of circEPSTI1 was found to be associated with lymph node infiltration, tumor size and TNM stage (190). A downregulation of hsa_circ_0025202 has been observed in breast cancer cells and tissues. Moreover, it was found to be in an inverse correlation with lymphatic metastasis and histological grade, which decreased cell proliferation, migration, colony formation, increased cell apoptosis and rendered cells sensitive to tamoxifen (TAM) treatment. Hsa_circ_0025202 regulates the expression and activity of FOXO3a by absorbing miR-182-5p which then affects inhibition of tumor and TAM sensitization effects (191). Thus, hsa_circ_0025202 can be considered as a therapeutic target in HR-positive breast cancers patients, particularly undergoing TAM therapy.

It has been observed that circFOXO3 and tumor suppressor genes are downregulated in breast tumor samples compared with non-tumor cells and tissues (18). An increased expression of circFOXO3 has been found to be associated with reduced cell viability and cell proliferation in the MDA-MB-231, a breast cancer cell line (42). It was observed that circFOXO3 could act as a miRNA sponge and play a critical role in cancer progression.

The circSMARCA5 expression was reduced in breast cancer tissue compared with its host gene *SMARCA5* (83). An induced expression of circSMARCA5 was observed to illicit drug sensitivity in breast cancer cell lines. The circSMARCA5 can prevent the expression of its host gene and can enhance the drug sensitivity of breast cancer cells to cytotoxic drugs, implicating therapeutic potential of it in drug-resistant breast cancer cells.

Lung cancer. One of the prominent leading causes of health hazards and cancer-related mortality is lung cancer (192). With the increase in the number of patients with cancer, a greater number of patients are being diagnosed with multiple primary lung cancer. Diagnostic cases with similar histologies for intrapulmonary metastasis and multiple primary lung cancers become more complicated to be adequately detected with complete assurance of specificity. Due to this, designing a strategy for the treatment takes a longer time, and by that time, the condition of the patient has worsened. With the advancement of technology, targeted and specific drugs are being applied to treat lung cancers in the advanced stage. This approach shows positive and effective results in patients with lung cancer in advanced stages. However, the major challenge is detection at an early stage to make the process of treatment easier and more effective for the health of the patient. It is evident from previous studies that specific types of circRNAs are present abundantly in specific tissues. The presence of conserved sequences in circRNAs may contribute significantly to the occurrence of cancer, and it has noticeable clinical values for the development of cancerous cells in the lung (33,193).

Of late, a significant increase in the circARHGAP10 expression was reported in non-small cell lung cancer cells and tissues associated with poor prognosis. Knockdown of this circRNA resulted in decreased proliferation and metastasis, implicating its potential role in the treatment of lung cancer. CircRNA from the gene circ-ITCH was downregulated in lung cancer tissues compared with non-cancerous tissues (194). The expression of the parental cancer-suppressive gene, *ITCH*, was markedly elevated by the ectopic expression of circ-ITCH, inhibiting the proliferation of lung cancer cells by suppressing the Wnt signaling pathway. It was observed that circ-ITCH may have suppressed miR-214 and miR-7 by acting as a sponge in lung cancer cells (194). Furthermore, circRNA_100876 expression was also found to be upregulated in non-small cell lung cancer tissues compared with normal lung tissues (91). A decreased survival rate of patients was observed with elevated expression of circRNA_100876 compared with those with reduced expression. Thus, circRNA_100876 may be considered as a biomarker for lung cancer. In lung squamous cell carcinoma (LUSC), increased expression of circTP63 was found to sponge miR-873-3p, eliminating its suppressive

effect and elevating the expression of FOXM1. This event, in turn, upregulated CENPB and CENPA and caused cell cycle progression. Elevated expression of circTP63 was associated with higher TNM stage and increased tumor size in LUSC patients implicating its role in cancer prognosis. In lung adenocarcinoma, the expression levels of circRNA from gene *ACP6* were found elevated and associated with tumor growth and metastasis, implicating a novel target for lung cancer treatment (68). Application of circRNAs in the treatment of cancer, including lung cancer, may be possible after developing suitable vector systems in the coming future. However, concern related to the negative effect of circRNAs due to mistargeting is true and disturbing. This issue can be resolved by smartly designing the small interfering (si)RNAs to target specific circRNAs (in a localized tumor environment).

HCC. HCC prognosis is very poor due to the aggressiveness and reoccurrence rate of cancer. With the progress of HCC, several circRNAs have been reported to participate in the development and invasion of hepatoma. Bioinformatic data analysis has revealed that several circRNAs can regulate the expression of miR-181a-3p. The miR-181a-3p can regulate the enzyme O(6)-methylguanine-DNA methyltransferase that is associated with DNA disruption. This possible link between HCC progression and circRNAs through the regulation of miRNA clearly implicates a relationship between the two (195). The expression levels of circβ-catenin were found to increase in liver cancer tissues than the nearby normal tissues (196). The circβ-catenin encodes a novel β-catenin isoform that promotes proliferation and migration of liver cancer cells *in vitro* and activates the Wnt signaling pathway that results in the reduction of tumorigenesis and metastasis *in vivo* (195). In addition, the hsa_circ_0005075 is more highly expressed in large liver cancer tumors than in smaller tumors, indicating its role in regulating tumor growth (95). Furthermore, the expression of hsa_circ_0005075 was found to be associated with the pathogenesis of patients with HCC. Analysis of pathways and gene ontology studies revealed it to be associated with cell adhesion, a crucial factor for cell proliferation and metastasis. The hsa_circ_0005075 decreases the miR-23b-5p expression in cancer by acting as a miRNA sponge (196). In HCC tissues and portal vein tumor thrombus metastasis, the expression of circ0003998 was upregulated (95), which acts as a sponge to miR-143-3p to reduce the suppressive effect of FOSL2 [epithelial-mesenchymal transition (EMT) related stimulator]. Moreover, to enhance the expression levels of EMT-related gene *CD44v6*, circ0003998 can bind to PCBP1 (94).

In comparison with adjacent liver tissues, HCC tissues show suppressed expression of hsa_circ_0001649 (104). siRNA-mediated inhibition of hsa_circ_0001649 increased the expression levels of pro-metastatic matrix metalloproteinases (MMP)9, MMP10 and MMP13, implicating its negative correlation with metastasis of HCC (164). Likewise, a suppressed expression of circHIAT1 was observed in HCC cell lines and tissues (197). The overexpression of circHIAT1 decreased HCC progression by regulating the miR-3171/PTEN axis. In HCC tissues, a significant increase in the expression of ciRS-7 has been reported (198). A release of miR-7 is known to be associated with HCC cell proliferation and metastasis (198,199). Therefore, it is likely that ciRS-7 may sponge miR-7 and regulate its downstream targeted genes. A recent study showed that the hsa_circ_0079929 expression was less in HCC tissues (97). The PI3K/AKT/mTOR signaling pathway was found to be responsible for the inhibitory effect of hsa_circ_0079299. Another circRNA, circ-0051443, was significantly downregulated in plasma exosomes and tissues (96). It was reported that circ-0051443 from exosomes was able to act as a sponge for miR-331-3p to promote BAK1 expression resulting in the inhibition of the progression of HCC (96). CircRNA derived from the genes *SHPRH* and *ZKSCAN1* were found to be downregulated in HCC cells as compared with non-cancerous cells (78,200).

Osteosarcoma. An abnormal expression of circRNA has been reported in patients suffering from osteosarcoma, and the overall survival rate is relatively low. An increased expression of circLRP6 was observed in osteosarcoma, causing a shorter disease-free and overall survival (105). CircLRP6 binds to LSD1 and EZH2 and acts as an oncogene to suppress KLF2 and APC expression levels. The downregulation of circ-PVT1 can reduce the encoding of a classical multidrug resistance-associated gene (ATP binding cassette subfamily B member 1), implying circ-PVT1 to be a more efficient diagnostic marker than alkaline phosphatase for osteosarcoma (124). High-throughput analysis revealed abnormal expression of circ-5'-nucleotidase cytosolic II in osteosarcoma, and it was found to be involved in regulating miR-488 and stimulating tumor cell growth and metabolism (201).

Samples from patients with osteosarcoma show comparatively more upregulated expressions of circUBAP2 than non-cancerous cells. Higher expression of circUBAP2 results in inhibition of apoptosis (202). It was revealed to enhance the expression of SEMA6D to improve the cisplatin resistance by sponging miR-506-3p and activating the Wnt signaling pathway (103).

CRC. During the differential expression screening of circRNAs in CRC tissues and normal tissue samples, circCCDC66 was observed to regulate various pathological processes, such as invasion, migration and anchorage-independent growth (48). High expression of hsa_circ_001569 has been observed in CRC compared with non-cancerous tissues (116,203). It was suggested that hsa_circ_001569 via miR-145 could promote cell proliferation and invasion in CRC via blocking the downregulation of E2F5/BAG4/FMNL2. Likewise, in lung cancer, a reduced expression of circITCH was observed in colorectal tissues compared with adjacent normal tissues (127). Previously, it has been shown that circ-ITCH possesses sponge activity for miR-7, miR-214 and miR-20a in CRC (127). These three miRNAs have been reported to be involved in regulating the cell cycle, including *cyclin D1* (a proliferative target gene). The circ-ITCH expression may block the gene expression of the Wnt signaling pathway like cyclin D1 and c-Myc, implicating its role in regulating the Wnt signaling pathway and thus in cell proliferation and migration (127).

An increased expression of hsa_circ_0000069 was reported in CRC. It was identified that siRNA-mediated inhibition of hsa_circ_0000069 suppressed the cell proliferation, migration and invasion, and exerted cell cycle arrest in HT-29 cells. Similarly, a high expression level of the

circ-BTG3 associated nuclear protein (BANP) was observed in CRC (123). A siRNA-mediated knockdown of circ-BANP reduced the cell proliferation of CRC. In addition, the knockout resulted in the downregulation of phosphorylated (p)-protein kinase B (Akt), involved in the regulation of cell cycle and survival. This points toward the involvement of circ-BANP in the phosphoinositide-3 kinase (PI3K)/Akt signaling pathway in CRC (123).

In CRC cell lines, a downregulation of hsa_circ_001988 was observed compared with normal colon mucosa (120). The expression level was found to be associated with the perineural invasion and cancer cell differentiation. The characteristic of perineural invasion is a marker for CRC prognosis in patients, suggesting hsa_circ_001988 as a potential biomarker for CRC prognosis.

Glioma. In case of morbidity and mortality related to cancer, glioma is one of the most common primary form of cancer. By performing deep sequencing in 10 pathologically diagnosed glioblasts, an upregulation of circ-FBXW7 was observed (107). The circ-FBXW7 was revealed to regulate the expression of a novel 21-kDa protein, designated as FBXW7-185aa. Overexpression of FBXW7-185aa suppressed the proliferation and acceleration of cell cycle in glioblast cell lines while promoting malignant phenotypes on the deletion of FBXW7-185aa, implicating a positive correlation with the overall survival of patients with glioblastoma (107). In glioma tissues and cell lines, a significant increase in circSCAF11 expression was observed (108). Moreover, a poor clinical outcome in glioma patients was found to be related to the ectopic overexpression of circSCAF11. The study revealed that miR-421/SP1/VEGFA axis is utilized by circSCAF11 to exert its tumorigenic effect in glioma (108). Gliomagenesis is enhanced in glioblastoma and oligodendroglioma due to the increased expression of a circRNA from the gene *VCAN* (204). However, cirZNF292 was found to be downregulated in patients with glioma (58). In a few cases, circRNAs can absorb proteins to affect tumorigenesis, apart from acting as miRNA sponges. For example, highly expressed circCPA4 in glioma tissues is proposed to function as a sponge for let-7 and regulate the translation of CPA4 and glioma progression. In human glioma cells, an upregulated expression of circTTBK2 was reported (115). Increased expression of circTTBK2 was found to be responsible for enhanced cell proliferation, migration and invasion. circTTBK2 acted as a sponge for miR-217, and the overexpression of miR-217 into the glioma cells was able to reverse the circ-TTBK2-induced progression of glioma. CircRNAs have also been reported to encode certain proteins that are involved in tumor progression. circ-SHPRH was shown to regulate the expression of SHPRH-146aa (a 17 kDa truncated protein), and the expression of both is low in glioma (205). Increased expression of SHPRH-146aa prevents the degradation of full-length SHPRH protein from proteasomal degradation. Stabilized SHPRH protein ubiquitinates proliferating cell nuclear antigen as an E3 ligase, resulting in inhibition of cell proliferation and tumorigenicity (205).

Ovarian cancer. From the data of RNA-seq analysis, it was found that expression of circRNAs varies at different stages of ovarian cancer, and it has been observed that the expression of circRNA is higher in ovarian cancer cell lines than the surface epithelial cells of the ovary that are made immortalized normally (63). A faster cell proliferation rate was found in the surface epithelium of ovarian cells that are made immortalized than the cell lines of ovarian cancer, which facilitates the accumulation of circRNAs within a short time (60). In ovarian cancer tissues resistant to cisplatin, the expression levels of circRNA, CDR1as were found substantially downregulated (206). It was observed that CDR1as utilizes the miR-1270/SCAI signaling pathway to exert a sensitizing effect in cisplatin-resistant ovarian cancer. Another circRNA, circPLEKHM3, was also found suppressed in ovarian cancer tissues compared with non-cancerous tissues (113). CircPLEKHM3 was reported to act as a sponge for miR-9 and thus inactivating AKT1 signaling by regulating the expression of BRCA1, DNAJB6 and KLF4. It was suggested as a prognostic marker as well as a therapeutic target for ovarian cancer. In ovarian cancer cell lines, upregulated expression of hsa_circ_0061140 was observed. A deletion of hsa_circ_0061140 inhibited the cell proliferation and process of migration in ovarian cancer. It was shown that hsa_circ_0061140 could sponge miR-370 to inhibit the expression of FOXM1 (114). Another circRNA, hsa_circ_0051240, was also reported to be significantly upregulated (207). hsa_circ_0051240 was found to induce cell proliferation and migration in ovarian cancer by inhibiting the miR-637/KLK4 axis. An increased expression of circRNA, circWHSC1, was found to be associated with proliferation, migration and invasion of ovarian cancer cells. This possibly occurs due to the fact that circWHSC1 can sponge miR-1182 and miR-145 to enhance the MUC1 and hTERT expressions (115).

Bladder cancer. A number of studies have been performed to analyze circRNA expression in bladder cancer. Through RNA-sequencing analysis of bladder cancer tissues, the expression levels of circRNA, circSLC8A1, were found downregulated (132). It was reported that circSLC8A1 may act as a tumor suppressor by sponging miR-130b and miR-494 and regulating the downstream target gene, *PTEN*. During bladder cancer progression, androgen receptor-mediated regulation of circRNA, circFNTA was reported (134). Androgen receptor-mediated increased expression of circFNTA was related to the sponging of miR-370-3p and inducing the expression of its host gene *FNTA*. This causes activation of KRAS signaling in bladder cancer cells, rendering them sensitive to cisplatin. It was suggested that to suppress metastasis and induce chemo-sensitivity in bladder cancer cells, circFNTA may be considered as a therapeutic target. Microarray analysis of bladder carcinoma reported dysregulation of 469 circular transcripts compared with normal tissues (208). Among them, the aforementioned study reported that circRNA, circTCF25, can enhance cell proliferation, migration, and invasion by sponging miR-103a-3p and miR-107. miR-103a-3p and miR-107 regulate the expression of CDK6, involved in cell proliferation and migration, thus implanting the regulatory role of circTCF25 in bladder carcinoma. Another microarray analysis of bladder carcinoma revealed that the expression level of circRNA-MYLK was upregulated (61). CircRNA-MYLK was reported to sponge miR-29a and enhance the expression of its target gene, *VEGFA*, promoting EMT and progression of bladder cancer (61). In urothelial carcinoma of the

bladder, advanced clinical stage and survival rate of patients were positively associated with the upregulation of circRNA, circPRMT5 (209). The circPRMT5/miR-30c/SNAIL1/E-cadherin axis was found to be critical for the progression of urothelial carcinoma of the bladder.

Significant downregulation of circRNA, hsa_circ_0018069, was observed in bladder cancer tissue (131). Bioinformatics analysis revealed that it may have an anticancer role by modulating focal adhesion and calcium signaling pathways. It was shown to have an interaction with miR-181b-5p, miR-23c, miR-34a-5p, miR-3666 and miR-454-3p. Similarly, a downregulated expression of circLPAR1 (hsa_circ_0087960) was observed in muscle-invasive bladder cancer (135). The circLPAR1 was revealed to act as a sponge for miR-762, and its knockdown increased invasion and metastasis of muscle-invasive bladder cancer. A downregulation of circRNA, circMTO1, was found to be positively associated with the metastasis of bladders cancer and poor survival of patients (210). circMTO1 was shown to sponge miR-221, and its overexpression suppressed the E-cadherin/N-cadherin pathway to inhibit EMT in bladder cancer cells. Through qPCR analysis, a substantial decrease in the expression of circRNA, hsa_circ_0000285, was reported in bladder cancer tissues compared with normal tissues (130). Moreover, patients with cisplatin-resistant bladder cancer had low expression of hsa_circ_0000285 compared with cisplatin-sensitive bladder cancer patients. Its expression was found to be associated with lymph node metastasis, tumor size, distant metastasis and TNM stage. The expression of circRNA, circBCRC3, is suppressed in bladder cancer tissues (128). Ectopic expression of circBCRC3 causes the proliferation of bladder cancer cells. CircBCRC3 was shown to sponge miR-182-5p and regulate the expression of cyclin-dependent kinase inhibitor 1B (p27).

Gastric cancer. Gastric cancer is considered the fifth most deadly form of cancer due to associated high morbidity and mortality rates (738,000 individuals succumb every year as reported in 2014) (211). Several studies have highlighted the dysregulation of circRNAs in gastric cancer progression. Bioinformatics analysis revealed that the expression level of circRNA, circ-DONSON, was upregulated in gastric cancer tissues compared with normal tissues (122). The elevated expression of circ-DONSON was reported to be associated with lymphoid metastasis and advanced TNM stage. Due to the nuclear localization of circ-DONSON, circ-DONSON was hypothesized to act as a sponge for miRNA. It was reported to involve the NURF complex to the promoter site of SOX4 and regulate its transcription, involved in gastric cancer malignancy (122). Analysis of two circRNA databases and qPCR analysis revealed that circRNA, hsa_circ_002059, is considerably downregulated in gastric cancer tissues compared with normal tissues (141). The plasma of postoperative patients with gastric cancer showed different levels of hsa_circ_002059 compared with plasma from preoperative patients with gastric cancer, suggesting it to be a potential biomarker for gastric cancer. An overexpression of circRNA, ciRS-7, was observed in 102 gastric cancer tissues compared with normal tissues, and its upregulation was found to be associated with poor patient survival (142). Furthermore, miR-7-induced tumor suppression was inhibited by the overexpression of ciRS-7 in gastric cancer cell lines. ciRS-7 involves the PTEN/PI3K/AKT signaling pathway to mediate aggressive oncogenic phenotype in gastric cancer cells. Similarly, the expression level of another circRNA, circNRIP1, was found to be elevated in gastric cancer tissues (142). A deletion of circNRIP1 in gastric cancer cells resulted in suppressed proliferation, migration, invasion, and decreased the levels of AKT1. The circNRIP1 was found to positively affect gastric cancer development by utilizing the circNRIP1-miR-149-5p-AKT1/mTOR axis.

Another circRNA that has been found to be upregulated in gastric cancer cells is circPVT1 (53). The circPVT1 has been revealed to sponge the member of the miR-125 family and promote cell proliferation in gastric cancer cells, making it a potential biomarker for gastric carcinoma. From the analysis of the GEO database, a novel circRNA, circFAT1(e2) (hsa_circ_0001461), was identified (144). A downregulated expression of circFAT1(e2) was observed in gastric cancer tissues, and it was found to be related to the overall survival rate of patients with gastric cancer. CircFAT1(e2) was found to regulate the expression of tumor suppressor gene *RUNX1* by acting as a sponge for miR-548g in gastric cancer cells. By controlling the expression of miR-548g in the cytoplasm and interacting with Y-box binding protein-1 in the nucleus, circFAT1(e2) was able to inhibit gastric cancer progression. Another circRNA, circPSMC3, was found to be downregulated in gastric cells and plasma from patients with gastric cancer (212). A suppressed expression of circPSMC3 was found to be associated with a shorter survival rate of patients and higher TNM stage. CircPSMC3 could modulate the expression of Phosphatase and Tensin Homolog by sponging miR-296-5p and further suppressing the gastric cancer progression. Screening for potential circRNAs from 17 gastric cancer tissues by RT-qPCR and 80 paired gastric cancer tissues by fluorescence *in situ* hybridization (FISH) revealed significantly lower expression of circRNA, circYAP1, in gastric cancer tissues compared with adjacent normal tissues (213). CircYAP1 inhibited the gastric cancer progression by sponging miR-367-5p to inhibit the expression of $p27^{Kip1}$, suppressing the progression of gastric cancer. In gastric cancer tissues and cell lines compared with normal gastric tissues, the expression levels of hsa_circ_0000096 (circHIAT1), were found to be downregulated (67). On deletion of circHIAT1 in gastric cancer cells, the cell proliferation and migration were inhibited, and the expression levels of cyclin D1, CDK6, MMP-2, and MMP-9 were substantially reduced. It was revealed that the expression of Ki67 and VEGF were decreased in gastric cancer xenograft nude mouse model in a dose-dependent manner after the knockdown of circHIAT1. An analysis of gastric cancer tissues and cell lines by RT-qPCR showed that circRNA_0023642 was significantly upregulated (147).

A suppressed expression of circRNA_0023642 was found to be associated with tumor inhibitory effects such as suppressed cell proliferation, migration, invasion and induction of apoptosis. CircRNA_0023642 was found to regulate the EMT signaling pathway and act as a promoter for metastasis in gastric cancer. RNA sequencing and bioinformatics analysis of gastric cancer tissues identified circRNA_LARP4 (circLARP4) as a sponge for

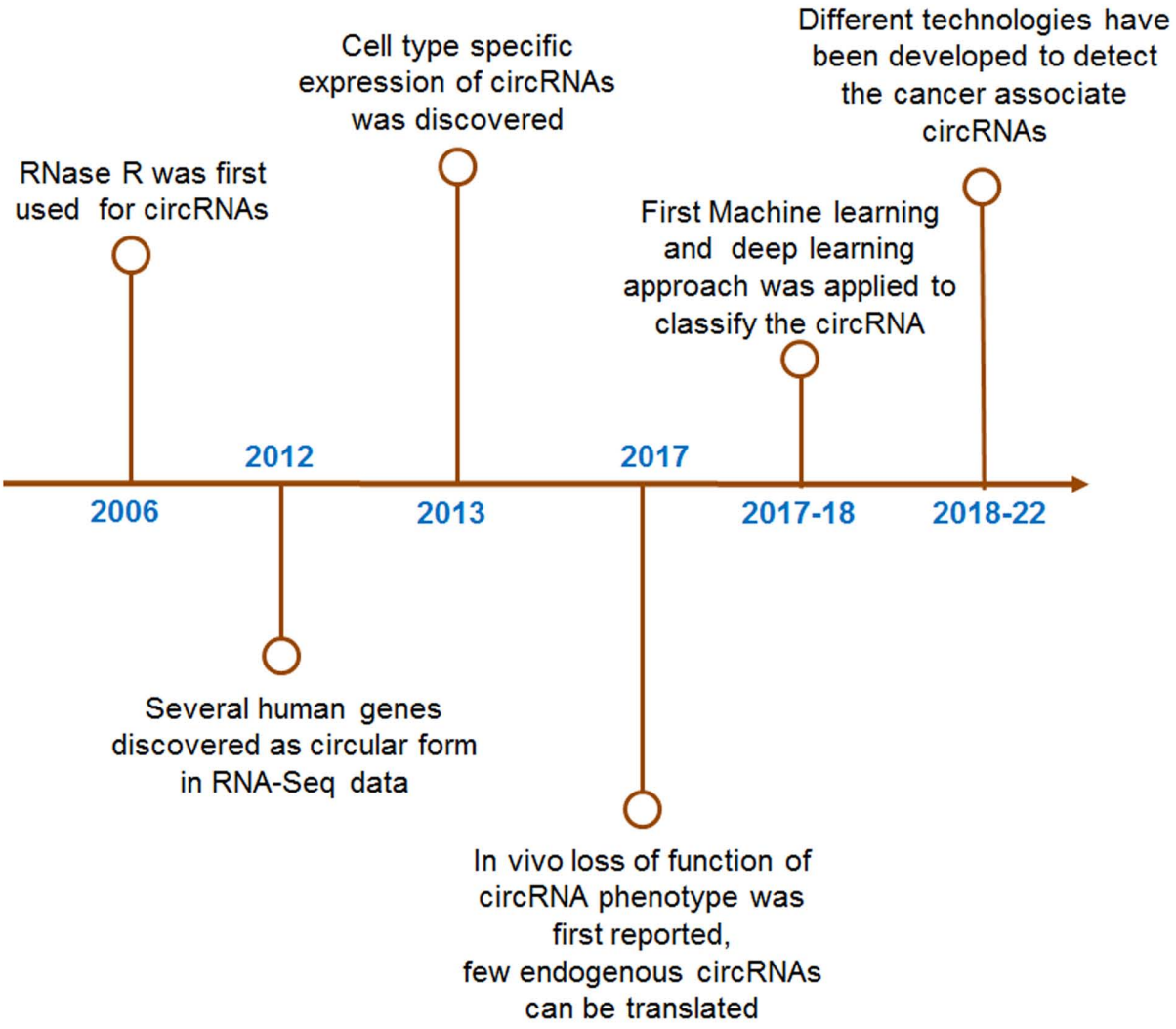

Figure 5. Timeline shows different developed technologies for circRNA. Technologies for circRNA have been developed in different directions such as molecular biology based technologies (Ribo-Zero and RNase R technique), computational biology based technologies (deep learning and machine learning for circRNA identification) and clinical technologies (detection of triple-negative breast cancer using circRNA) (circRNA, circular RNA).

miR-424 (148). Ectopic expression of miR-424 was shown to promote proliferation and invasion in gastric cancer cells by modulating the large tumor suppressor kinase 1 gene. Utilizing FISH in tissues of patients with gastric cancer, an elevated expression of circRNAs, circDLST, was observed (149). A deletion of circDLST inhibited cell proliferation, cell invasion and metastasis, while overexpression of circDLST rendered opposite effects. circDLST was shown to favour tumorigenesis and metastasis in gastric cancer cells by activating the NRAS/MEK1/ERK1/2 signaling via sponging of miR-502-5p. Activating HuR-derived circRNA, circ-HuR (hsa_circ_0049027) was found to be downregulated in gastric cancer cells (150). Circ-HuR downregulates the expression *Hur* gene and suppression of gastric cancer progression by interacting with CCHC-type zinc finger nucleic acid-binding protein.

Next-generation sequencing profiling showed abundant circRNA, circOSBPL10 (derived from the *OSBPL10* gene), in gastric cancer cells (151). A knockdown of circOSBPL10 inhibited proliferation, migration and invasion of gastric cancer cells. circOSBPL10 was found to promote tumor growth and metastasis by utilizing the circOSBPL10-miR-136-5p-WNT2 axis.

A downregulation of circRNA, hsa_circ_0000745, was observed in gastric cancer tissues and plasma samples (152). In gastric cancer tissues, the expression level of hsa_circ_0000745 was associated with tumor differentiation, while in plasma, it was found to be associated with the tumor-node-metastasis stage. The expression level of hsa_circ_0000745 in plasma along with carcinoembryonic antigen was suggested as a potential diagnostic marker for gastric cancer malignancy. Another circRNA that has been projected as a biomarker for gastric cancer is hsa_circ_0000520 (153). A significantly reduced expression of hsa_circ_0000520 was observed in gastric cancer tissues, plasma and gastric cancer cell lines. Moreover, hsa_circ_0000520 was reported to have an interaction with a total of 9 miRNAs.

11. Role of circRNAs in immunotherapy and tumor immunology

The current outlook is to understand the role of the immune system in tumor biology and how it participates in identifying and destroying cancer cells. A total of two types of tumor antigens are expressed by tumor cells which are

tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). Generally, both tumor and normal cells express TAAs, but TSAs are only expressed in tumor cells (214). The immune system responds to the tumor cells by targeting TSAs or TAAs. Malignant tumor cells are recognized by the immune system as a foreign body during immunosurveillance and are eliminated (215). Previous studies have revealed that tumor cells adopt certain immune evasive mechanisms to avoid immune surveillance and establish a microenvironment analogous to normal tissue (215,216). The tumor microenvironment (TME) is a complex, dynamically regulated ecosystem harboring cancerous cells, surrounding stromal cells and immune cells (217). Immune cells play a critical role during cancer progression and are the most significant cell population in TME. The population of immune cells in TME usually comprises $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, T regulatory cells, B cells, dendritic cells, natural killer cells (NK), tumor-associated neutrophils, macrophages and myeloid-derived suppressor cells. A complex composition at the cellular and molecular level, including signaling molecules from the immune cells, forms a tumor immune microenvironment (TIME), closely associated with an adaptive or innate immune response to cancer cells (218,219). Previous studies have highlighted that cancer cells can modulate the immune cells in their favor and assist in immune escape and cancer progression. Thus, targeting the cross-talk between cancer and immune cells in TME may be a potential approach to treat cancer (217,218).

Recently, the roles of circRNAs in the TME have been recognized, appreciated and reviewed (220,221). CircRNAs have been shown to modulate the function of immune cells like macrophages, neutrophils and NK cells in various types of cancer (222), also discussed under circRNAs in various types of cancer in the present review. Moreover, promoting immunosuppression and inducing resistance against cancer therapies has also been attributed to the circRNAs (223,224). In pancreatic cancer tissues, overexpression of circPTPN22 was found to be associated with cancer size. circPTPN22 was shown to stimulate STAT3 acetylation, resulting in immunosuppression. A knockdown of circPTPN22 was shown to induce high immune cell infiltration (NK cells, $CD8^+$ T cells, $CD4^+$ T cells and γδT cells) of tumor and suppress tumor growth. CircRNAs (circ0000831, circ005019, circ0031584 circ0006935 and circ0001730) have been revealed to induce changes in the TME of recurrent nasopharyngeal carcinoma. Altered distribution of immune cells and a decline in the ratio of $CD4^+/CD8^+$ T cells were observed in the presence of these circRNAs (225). Targeting T cell activation by inhibiting the checkpoints such as the PD-1/PD-L1 pathway is termed checkpoint immunotherapy (226). In lung cancer tissues, the expression of circ-CPA4 and PD-L1 is reportedly high, while the expression of miR-let-7 is low. High expression of PD-L1 has been observed to induce tumor immune escape, resistance to therapy and cancer progression (227). circ-CPA4 was revealed to regulate the activation of $CD8^+$ T cells in TIME by let-7 miRNA/PD-L1 axis. Elevated expression of circ-CPA4 was shown to inhibit miR-let-7 and promote exosomal PD-L1 secretion, resulting in the inactivation of $CD8^+$ T cells and increased resistance against cisplatin (228). In lung adenocarcinoma, circRNA, circRNA002178 (contained in tumor exosomes) can induce the expression of PD-1 receptors in $CD8^+$ T cells, inactivating $CD8^+$ T cells and promoting tumorigenesis (229). CircRNA, circ-LAMP1, is overexpressed in T cell lymphoblastic lymphoma and inhibits cell apoptosis. It promotes cell growth by sponging miR-615-5p [targets domain receptor tyrosine kinase 2 (DDR2)] and activating DDR2, a family member of receptor tyrosine kinase and closely associated with tumor progression (230).

Tertiary lymphoid structures (TLS), closely associated with B cells, are present in a wide number of cancer tissues (231). A number of studies have acknowledged the importance of TLS in tumor immunotherapy. CircRNAs have been shown to mediate the antibody response directly or indirectly. CircRNA NC_006099.4:15993284|16006290 and circRNA NC_006099.4:1 6132825|16236906 related to parental gene, *NFATC2* was shown to mediate B cell proliferation via Foxp1 pathway (232). A study in plasma of patients with HCC revealed that hsa_circ_0064428 was associated with high tumor-infiltrating lymphocytes (TILs), and it may function as a key regulator of TIL formation (233). The role of circRNAs in regulating NK cells has also been reported. The expression of the inflammatory gene, *MMP2*, is regulated by hsa_circ_0008433 by sponging miR-181c-5p and miR-181b-5p, leading to attack of NK cells on arterial fibers causing progression of the aneurysm (234). In pancreatic cancer, the overexpression of circ_0000977 results in sponging of miR-153, resulting in the accumulation of HI1FA. This causes inhibiton of NK cell-mediated lysis, promoting immune escape properties in pancreatic cancer cells (235). Recent discoveries revealed that circRNAs regulate the activation of macrophages. A circRNA microarray analysis for the expression of circRNAs in two different polarizing macrophages (M1 and M2) activation revealed differential expression of circRNAs. CircRNAs, circRNA003780 circRNA010056, and circRNA010231 were highly expressed in M1 macrophages, while the expression of circRNA-003424, circRNA-013630, circRNA-001489 and circRNA-018127 was higher in M2 macrophages. Differential expression of circRNAs in two subtypes of macrophages having a distinct function in tumor progression demonstrates the role of circRNAs in the differentiation and polarization of macrophages and thus a potential in tumor immunotherapy (236). Higher expression of another circRNA, circ-CDR1as, was found to be associated with a higher ratio of M2 macrophages implicating a role of circ-CDR1as in TME via M2 macrophages (237).

TME has to be reprogrammed for a potent therapy against cancer, and thus identification of novel therapeutic which can influence TME is a prerequisite. CircRNAs have been found to regulate the TIME by influencing the regulatory mechanism of immune cells such as T cells, B cells, macrophages and NK cells. Though tumor immunotherapy plays a substantial role in the treatment of cancer, the application of circRNAs in tumor immunotherapy remains in its fancy state. To date, no preclinical trials have been reported for circRNAs alone as therapeutic targets or along with vectors in cancer. However, it is likely that with the ongoing efforts in the field of circRNAs and TME, novel immunotherapy involving circRNAs can be expected.

12. Technological landscape of circRNAs for cancer

Different novel bioinformatics algorithms and high throughput technologies have been developed to detect the novel circRNAs in cancer (158). High-throughput RNA-seq technologies can be used for the discovery of circRNAs. Like, RNA-seq technologies are being employed and being further developed properly for the discovery of circRNAs, which can profile non-polyadenylated transcripts (238). At present, it has been observed that Ribo-Zero and RNase R are two standard gold techniques for discovery of circRNAs (158). This first gold standard technique, RNase R, has been developed for the enrichment of circRNAs from the sample, which is a significant milestone for degrading linear RNAs and enriching circRNAs within samples (31). At the same time, Ribo-Zero has also helped to enrich circRNAs. It can deplete the rRNAs and preserve linear transcripts (239). At the same time, bioinformatics technology has developed several tools and servers to classify circRNA from other noncoding RNA. In this direction, machine learning and deep learning approaches have been used to classify the circRNAs (240,241).

Scientists are developing new circRNA-based technology and applying the patents for these developed technologies (Fig. 5) (158). Recently, Wesselhoeft *et al* (5) developed a technology for circRNA-related transfer vehicles. The technologies have been developed by a team of researchers from MIT, and patented in the USA (USA patient no: US20210371494A1). Researchers from China have filed Chinese patents claiming prostate cancer therapy can be treated using one circRNA (circCRKL). Jinshan Hospital of Fudan University has also applied for the patent (Chinese patent no. CN109908369A). Again, technology was developed to detect triple-negative breast cancer using specific circRNA (Chinese patent no. CN107254519B). Another patent was filed from China to develop a new technology that describes circRNA (hsa _ circ _0004872) for use in gastric cancer treatment. Shandong University has filed the patent (Chinese patent no. CN110117658B).

13. Potential of circRNAs as biopharmaceuticals

For pharmacological applications, the therapeutic RNA products should possess certain desirable characteristics such as stability, quality, safety and the ability to retain the biological activity until it reaches the site of action (specific organelles, cytoplasm, or nucleus) (242-244). Rapidly expanding functional abilities of RNAs have been projecting them as next-generation therapeutics for numerous diseases. With the progress in the field of circRNAs in cancer biology, a number of patents have been issued in several countries (Fig. 6). A list of patents for circRNAs in cancer has been summarized in Table IV. Moreover, with the advent of new technologies on RNA delivery systems like lipid-based nanoparticles, polymer-based nanoparticles, and metal nanoparticles, the delivery of circRNAs to the site of action can be made more feasible (244). It is expected that in the near future this next generation of therapeutics will be available in the commercial market for the treatment of several types of cancer.

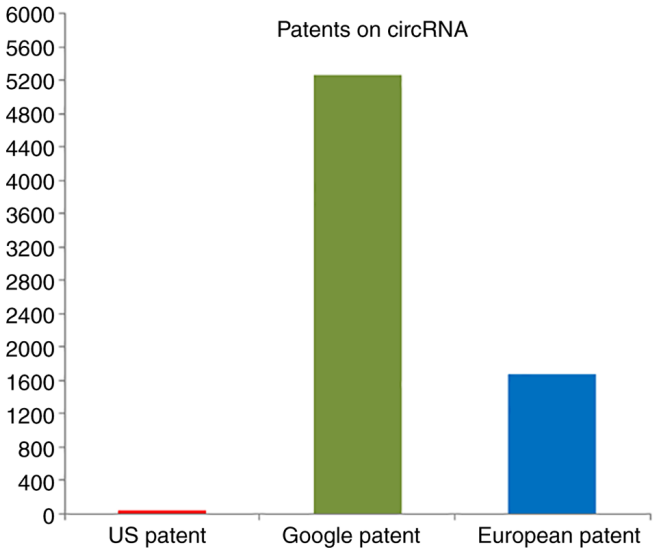

Figure 6. Bar diagram shows the numbers of circRNA patents. Data collected from the US patent (www.uspto.gov), the Google patent (www.google.co.in/patents) and the European patent database (www.epo.org) using 'circular RNA' as keyword. The search was performed through quick search. circRNA, circular RNA.

14. Future perspectives

At the initial stage of research, circRNAs were considered to be the errors in the process of RNA splicing. Gradually with the progression of research in the field of bioinformatics, several endogenous circRNAs were found and identified with the involvement of RNA-seq approaches to reveal the mystery of circRNAs, but it needs more research to find out the specific mechanism behind the biosynthesis of circRNA and its significant role in the pathogenesis of cancer. By the development of certain tools like CIRI (51), find-circ (61), MapSplice (208), circRNA finder (53), Acfs (245) and CIRCexplorer (6) has made the work of finding circRNA markedly easier and faster, and their role in specific tissues was also discovered. It has been found that circRNAs are highly conserved in their sequences within the cells of mammals. As circRNAs are found to be tissue-specific, thus ideally, they can be targeted in such a way that there will be no interference with the liner mRNA (246). CircRNAs are recognized as the biomarkers for cancer, thus with the involvement of a larger clinical sample size, their sensitivity and efficiency can be figured out as the potential targets in different individuals at different stages of cancer for getting a validated result (19,52). With more in-depth analysis and the progress of advanced scientific technologies, the biological functions of circRNAs would be elucidated in the near future. Moreover, circRNAs have the potential role in influencing the choice of therapy as they may be favored for cancer resistance to chemotherapy. As discussed earlier, in various types of cancer resistant to certain drugs, the expression of certain circRNAs has a regulatory role in cancer resistance to drugs. However, advanced research is required for their site-specific delivery and understanding the complete mechanism of regulation of tumor biology. It would be interesting to decipher the role of circRNAs as

Table IV. A list of patents of 'circRNAs' having a role in cancer regulations.

Sl. no.	Patent no.	Country of origin	Patent name/Title
1.	CN107586848A	China	Glioma prognostic marker circ8:127890589 | 127890998 and application.
2.	WO2021092331A1	USA	Targeting circular PCMTD1 in leukaemia with P53 mutations and/or BCR/ABL fusions.
3.	CN106148494A	China	Application of circRNA in colorectal cancer biomarkers.
4.	JP2020514370A	Japan	CircRNA and immune checkpoint inhibitors for combination anticancer therapies.
5.	WO2021128516A1	China	Application of circRNA PVT1 and peptide in tumor growth prediction, metastasis prediction, prognostic assessment and treatment.
6.	CN109161595A	China	CircRNA marker for liver cancer diagnosis.
7.	US2021069310A1	USA	Endogenous tumor-derived circRNA and proteins thereof for use as vaccine.
8.	CN112159848A	China	Application of circRNA as gastric cancer diagnosis biomarker and prognosis evaluation reagent.
9.	CN111876488A	China	CircRNA marker hsa_circ_0006670 and application thereof in prostate cancer diagnosis.
10.	CN109097477B	China	CircRNA marker for breast cancer diagnosis and application thereof.

circRNA, circular RNA.

biomarkers and or therapeutic targets for the treatment of cancer.

15. Conclusions

It can be summarized that with the advancement of research and technology, the role of circRNAs in cancer treatment has come into recognition which may help design therapeutic and diagnostic strategies to combat the problem of cancer. But in the current scenario, very little is known regarding functions of circRNAs, and a lot of research must be carried out to project them as therapeutic targets for cancer treatment. However, it is a very new and promising field of cancer research. The aspect of post-transcriptional modification has not been revealed properly yet in circRNA biology. Activity and stability of RNA vary due to chemical modifications such as inosine to adenine, N6-methyladenosine, 5-methylcytosine, N1-methyladenosine and 5-hydroxymethyladenosine. Thus, the activity of circRNA is likely to get hampered due to aberrant modification of RNA and thus needs further validation for safe efficacy in clinical trials. According to the data that has been revealed to date, circRNAs appear to be a promising structural element as an efficient biomarker for cancer and potential and valuable therapeutic targets for cancer treatment.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

ARS researched data for the article and wrote the manuscript. SB substantially contributed to the discussion of the topic and contributed to writing of the article. MB and CC contributed to the editing, generating the figures and tables of the manuscript. AS reviewed the manuscript. SSL and CC reviewed and edited the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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