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REVIEW

Circulating circRNAs as Potential Biomarkers for Cancers

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ABSTRACT

Cancers are diseases with a high mortality rate worldwide. In order to better diagnose and improve the survival rate, many studies have been conducted. In recent years, the role of non-coding RNAs in cancers has been confirmed, and circular RNAs (circRNAs) have attracted much attention. CircRNAs are involved in the occurrence and development of cancers with high stability. Experiments have shown that they can exist stably in peripheral blood. Therefore, the expression of circulating circRNAs can be detected to help diagnose cancers and reflect tumor progression. In this review, we summarized the role of circulating circRNAs in cancers and discussed their potential as biomarkers.

KEYWORDS

Circulating circRNAs; plasma; serum; diagnosis biomarkers; cancers

Abbreviations:

circRNAs:	Circular RNAs
miRNAs:	MicroRNAs
lncRNAs:	Long non-coding RNAs
RBP:	RNA binding protein
ceRNA:	Competitive endogenous RNA
RBM3:	RNA binding protein 3
GC:	Gastric cancer
Pol II:	Polymerase II
IRES:	Internal ribosome entry sites
ORFs:	Open reading frames
NSCLC:	Non-small cell lung cancer

LUAD: Lung adenocarcinoma
ROC: Receiver operating characteristic
OS: Overall survival
NPC: Nasopharyngeal carcinoma
AUC: Area under the receiver operating characteristic curve
CEA: Carcinoembryonic antigen
CA199: Carbohydrate antigen199
CA724: Carbohydrateantigen724
EGC: Early gastric cancer
HCC: Hepatocellular carcinoma
AFP: Alpha-fetoprotein
CRC: Colorectal cancer
ESCC: Esophageal squamous cell carcinoma
TNM: Tumor-node-metastasis
PDAC: Pancreatic ductal adenocarcinoma
CA153: Cancer antigen-153
OC: Ovarian cancer
SOC: Serous ovarian cancers
EOC: Epithelial ovarian cancer
PCa: Prostate cancer
PSA: Prostate-specific antigen
BPH: Benign prostatic hyperplasia
CLL: Chronic lymphocytic leukemia
CML: Chronic myeloid leukemia
MM: Multiple myeloma
DLBCL: Diffused large B-cell lymphomaa

1 Introduction

Cancer, resulted from uncontrollable cell proliferation and differentiation, is one of the most lethal diseases suffered by a large number of people worldwide, leading to spike in death cases each year [1,2]. Today there are a lot of ongoing researches on diagnosis and treatment for cancers. Early detection and diagnosis of cancers may help increase the survival rate of patients, but the detection methods currently used in clinical are not sufficiently sensitive and specific to early diagnosis, which makes it imperative to find new biomarkers as soon as possible [3]. In recent years, many studies have confirmed that non-coding RNAs that mainly include microRNAs (miRNAs), long noncoding RNAs (lncRNAs) and circRNAs, etc., play an important role in tumor diagnosis [4] (Fig. 1).

CircRNAs refer to endogenous non-coding RNAs with a wide expression in the mammalian genome [5]. Initially observed in RNA viruses, circRNAs were deemed as a by-product of splicing-mediated splicing errors because of their low expression [6]. CircRNAs vary in types, and thousands of circRNAs have been identified in different categories of human cell [7]. CircRNAs have a covalent closed-loop structure without 5'-end cap and 3'-end poly (A) tail, which makes them more stable than linear RNA and less susceptible to degradation resulted from RNA exonuclease [8–10]. The function of circRNAs can be divided into five aspects: they can act as miRNA sponge, interact with RNA binding protein (RBP), act as autophagy regulators, regulate the transcription process and encode proteins [11–16]. Referring to the in-depth study on circRNAs, speculations of the correlation between abnormal function and the development of human diseases are made. Mounting evidence has shown that circRNAs have a close

correlation with cancers [17,18]. Since circRNAs evolve slowly with long half-life, and become highly stable on account of its circular structure, so they can stably exist in plasma, saliva, and other surrounding tissues as potential biomarkers with minimal invasiveness [19]. Studies have shown that circRNAs have half-lifes of more than 48 h, longer than lncRNA [20]. In this review, the functions of circRNAs and the roles of circulating circRNAs in cancers were inducted, and the feasibility of circulating circRNAs as biomarkers of cancers were discussed.

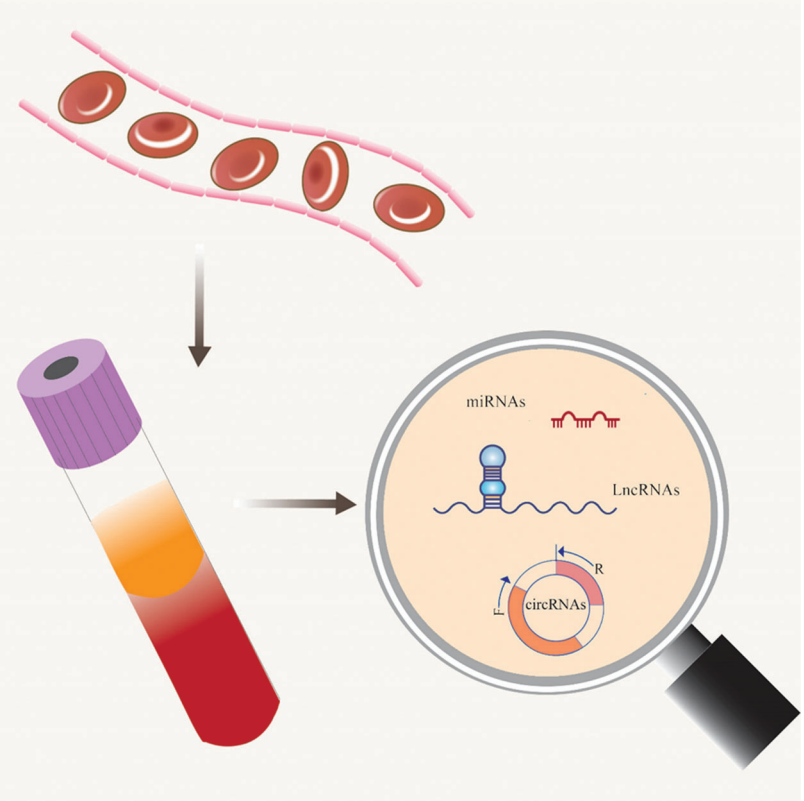

Figure 1: Non-coding RNA that can be detected in peripheral blood, including microRNA, lncRNA and circRNA

2 The Biological Functions of circRNAs

2.1 As microRNA Sponges

This is a well-studied function of circRNAs, which may act as miRNA sponges by indirectly regulating gene expression through binding of competing miRNAs [21]. CircRNAs regulate their activity by binding to miRNAs and then reduce their ability to target mRNA [22,23]. Compared with other competitive endogenous RNA (ceRNA), they have a higher binding capacity to miRNAs [24,25]. For instance, Chen et al. found that the upregulation of circ-MALAT1 increased JAK2, and it is known that circRNA acts as a miRNA sponge to regulate target gene expression [26]. CircRHOBTB3 is considered to be the sponge of miR-654-3p, which inhibits the growth of gastric cancers by activating the p21 signaling pathway [27] (Fig. 2a).

2.2 Interacting with RBP

RBP plays a vital role in a variety of cellular processes, such as cell function, transport, and localization, especially in the post-transcriptional regulation of RNA [28]. RBP can be used as a trans-acting factor that

regulates circRNAs biogenesis, and can also isolate, store, and classify RBP, thereby controlling intracellular positioning [2,29]. There is increasing evidence that circRNAs interact with RBP and participate in the regulation of gene expression. For example, the production of SCD-circRNA2 is dynamically regulated by RNA binding protein 3 (RBM3). By regulating the level of RBM3 or SCD-circRNA2, it is found that RBM3 relies on SCD-circRNA2 to promote the proliferation of HCC cells [30] (Fig. 2b).

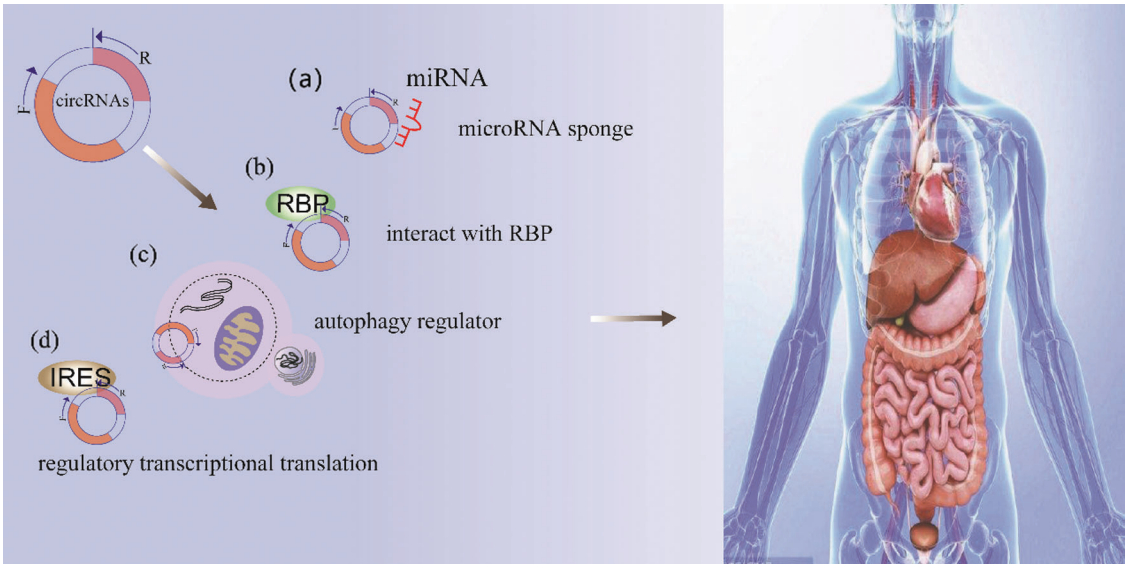

Figure 2: The biological function of circRNA (a) As microRNA sponges: circRNAs may act as miRNA sponges by competing for miRNAs binding and indirectly regulating gene expression (b) Interact with RBP: circRNAs interact with RBP and participate in the regulation of gene expression (c) As autophagy regulator: circRNA-mediated autophagy can promote the proliferation and invasion of cancer cells (d) Regulate the transcription and translation: (1) CircRNAs can regulate gene expression transcription or post-transcription level. (2) CircRNAs can encode regulatory peptides, and there may be hidden proteomes encoded by circRNAs

2.3 As Autophagy Regulator

Autophagy is a highly conservative and continuous self-degradation process that plays an important role in cellular stress response and survival [31]. This process usually occurs during tumorigenesis, progression, metastasis, and chemotherapy, leading to drug resistance in cancers treatment [32]. CircRNA-mediated autophagy can promote the proliferation and invasion of cancers cells [33]. Some studies have found that circRNAs are involved in cancer autophagy, affecting the occurrence and development of human cancers. For example, the over-expression of circ_0032821 inhibits autophagy of human Gastric cancer (GC) cells *in vitro* [13]. The studies of circRNAs in cancer autophagy are still in their infancy, and more researches are needed to verify their functions and mechanisms (Fig. 2c).

2.4 Regulating the Transcription and Translation

CircRNAs can regulate gene expression transcription or post-transcription level [34]. The circRNAs part in the nucleus acts as a transcription or splicing regulator, interferes with gene expression, and participates in other splicing and transcription processes [35]. CircRNAs in human cells can regulate the transcription of the parental gene in a cis-acting manner [5]. For example, the circRNAs produced by the ANKRD52 gene can form a complex with RNA polymerase II (pol II), and the complex binds to the promoter region of the

ANKRD52 to enhance transcription [36]. CircRNAs used to be considered non-coding RNAs, but later studies have found that circRNAs can participate in translation when they have internal ribosomal entry sites (IRES) or open reading frames (ORFs) [37,38]. CircRNAs can encode regulatory peptides, and there may be hidden proteomes encoded by circRNAs [8]. CircLgr4 encodes circLgr4-peptide for CRC targeted therapy [39]. The spanning junction open reading frame of circ-FBXW7 is driven by the internal ribosome entry site encoding FBXW7-185aa, and the expression of circ-FBXW7 is positively correlated with overall survival in glioblastoma patients [40] (Fig. 2d).

3 The Role of Circulating circRNA in Cancers

Compared with other methods, obtaining peripheral blood from patients is relatively simple and non-invasive. The expression of circulating circRNAs can be detected to diagnose cancers or predict the progress of cancers. Many studies have verified that the expression of circRNAs in plasma and serum is related to the development of cancers, and it is believed that circulating circRNAs can be used as biomarkers for cancer diagnosis and prognosis.

3.1 Respiratory System Cancers

3.1.1 The Role of Circulating circRNA in Lung Cancer

Lung cancer is the leading cause of cancer death worldwide, most of which is non-small cell lung cancer (NSCLC). NSCLC includes lung adenocarcinoma (LUAD), squamous cell carcinoma, and large cell carcinoma. LUAD accounts for approximately 50% of all types of lung cancer, and the 5-years survival rate is less than 20%. Therefore, it is necessary to find biomarkers for early diagnosis of LUAD [41–44]. In the current study, hsa_circ_0005962 in LUAD plasma and cells was up-regulated, while hsa_circ_0086414 was down-regulated. Based on the study results and the receiver operating characteristic (ROC), the authors believed that two circRNA molecules can improve the diagnostic accuracy of LUAD [45]. Hsa_circ_0013958 was further confirmed to be up-regulated in all LAUD plasma. Therefore, hsa_circ_0013958 can be used as a potential non-invasive biomarker for the early detection of LAUD [46]. Regarding the study of serum circRNA, the expression level of circMAN1A2 in the serum of lung cancer patients was higher than healthy controls. Considering that serum circMAN1A2 can be used as a serum biomarker for lung cancer [47]. Lu et al. [48] found that plasma hsa_circ_0001715 expression was an independent prognostic factor for overall survival (OS) of LUAD. Other studies have found that the effect of cisplatin combined with gemcitabine on NSCLC chemotherapy could be determined by detecting the expression of serum circPVT1 [49]. The above studies have shown that the expression of circulating circRNA in lung cancer can reflect the progress of cancers, but these studies are more common in LUAD, while other types of lung cancer are less.

3.1.2 The Role of Circulating circRNA in Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a malignant cancer that occurs in nasopharyngeal epithelial tissue, and most patients with NPC are already in middle-stage and late-stage at the time of diagnosis [50,51]. In order to diagnose NPC earlier, people have explored whether circRNAs in the blood could be used as non-invasive biomarker. CircMAN1A2 can be up-regulated in the serum of patients with NPC. The area under the receiver operating characteristic curve (AUC) of circMAN1A2 in the serum of patients is 0.911, indicating that it can be used as an effective diagnostic biomarker for NPC [47]. Compared with the healthy control group, circRNA_0000285 in serum samples of NPC patients increased significantly. Univariate and multivariate analysis indicated that circRNA_0000285 may be an independent prognostic factor for the prognosis of NPC patients, so it may be a new biomarker for NPC and participate in the radiosensitivity [52]. We believe that circulating circRNA can provide new ideas for the diagnosis of NPC.

3.2 Digestive System Cancer

3.2.1 The Role of Circulating circRNA in Gastric Cancer

GC is a major malignant cancer with high morbidity and mortality. Although this situation has been alleviated in recent years with the development of medical technology, the prognosis is still poor [53,54]. To date ,the five-years survival rate of advanced GC is very poor, so early diagnosis is important [55]. At present, gastroscopy is widely used for early detection of GC, but there would be omissions. The specificity and sensitivity of carcinoembryonic antigen (CEA), carbohydrate antigen199 (CA199), carbohydrateantigen724 (CA724) and other serum biomarkers which commonly used in clinical are not high enough, so new biomarkers need to be explored for use alone or in combination for early detection [56]. Some studies have found that the expression of plasma circRNA is different between GC patients and healthy people. For example, hsa_circ_0000520 is down-regulated in GC tissues, and the detection in plasma is also down-regulated. Besides, its expression in plasma is related to CEA [57]. There are some studies to prove the value of plasma circRNA in diagnosis. Hsa_circ_0021087 and hsa_circ_0005051 were down-regulated in GC tissues and plasma. There was a significant difference in the expression of plasma hsa_circ_0021087 between GC patients before and after the operation. So it can be used as a non-invasive biomarker for GC diagnosis [58]. Lu et al. [59] found that the expression of plasma hsa_circ_0006848 has a good diagnostic value, and the plasma level of hsa_circ_0006848 in postoperative patients is significantly higher than that in preoperative patients. Hsa_circ_0006848 in plasma may be a promising diagnostic biomarker for early gastric cancer (EGC) [59]. Besides, some people believe that plasma circRNA has higher diagnostic accuracy than tissues, and the combined circRNA has good diagnostic efficacy for GC [60]. In summary, circulating circRNA could be used as a diagnostic and prognostic biomarker for GC.

3.2.2 The Role of Circulating circRNA in Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is one of the most common malignant tumor in the world, with a high mortality rate [61]. Alpha-fetoprotein (AFP) is the most commonly used biomarker for HCC, but its specificity and sensitivity are not perfect [62]. Many studies have shown that HCC can be diagnosed by detecting the expression level of circRNA in plasma [63]. For example, hsa_circ_0027089 is up-regulated in the plasma of HCC patients compared with healthy people, and it can be used in combination with serum AFP as a biomarker of hepatitis B-related HCC [64]. Other studies have found that the plasma level of hsa_circ_0003998 in patients with HCC is significantly higher than that in patients with hepatitis B and healthy controls, and the plasma hsa_circ_0003998 level in postoperative patients is significantly lower than that in preoperative patients. Consequently, it can be used as a new potential biomarker for the diagnosis and prognosis of HCC [65]. There are similar studies in serum, for example, circRNA_101237 was up-regulated in the serum of HCC patients compared with the healthy controls. Additionally, univariate and multivariate analysis showed that serum circRNA_101237 level is an independent predictor of survival prognosis in HCC patients [66]. Other studies have pointed out that plasma circRNA can diagnose HCC. The experimental results showed that the level of plasma hsa_circ_0001445 can be used as an indicator for determining HCC [67]. High expression of serum circRNA_101237 is related to poor prognosis of liver cancers patients. Univariate and multivariate analysis can determine that serum circRNA_101237 level is an independent predictor of survival prognosis in HCC patients [68]. These studies could find that the expression of plasma or serum circRNA is different in healthy controls and HCC patients, which can be used in combination with serum AFP to diagnose and assess the stage of HCC.

3.2.3 The Role of Circulating circRNA in Colorectal Cancer

Colorectal cancer (CRC) is one of the most common malignant gastrointestinal cancers, and some patients will find liver metastases during examination [69]. Although the diagnosis and treatment methods have been mastered, the mortality of colorectal cancers is still high [70]. Early diagnosis may improve the

survival ability of CRC patients to a certain extent. The diagnostic efficiency of CEA and CA199, which are commonly used at present, needs to be improved, so it is necessary to explore new diagnostic methods to treat as soon as possible [71]. For example, circVAPA was up-regulated in the plasma of CRC patients by qRT-PCR, and circVAPA levels were related to the adverse clinical-pathological characteristics of CRC. The AUC is 0.724, indicating that the plasma level of circVAPA can be used as a promising biomarker for CRC detection [72]. The expression of hsa_circ_0007534 in the plasma of CRC patients was significantly increased compared with the healthy control group. The increased expression of hsa_circ_0007534 in plasma is associated with the clinical classification, metastatic phenotype, and poor differentiation of CRC patients. The high expression of hsa_circ_0007534 is positively correlated with the poor prognosis of CRC patients [73]. Plasma circ-STIL1 levels are related to tumor growth and progression. Plasma circCCDC66 and circ-ABCC1 levels are reduced in CRC precursor lesions. Considering circ-CCDC66 and circ-STIL can be used to diagnose early CRC [74]. In these studies, circRNAs were highly expressed in the plasma of CRC patients. The expression of plasma circRNAs in CRC could reflect the progress of the tumor, which can be used in combination with CA199 and CEA to diagnose CRC.

3.2.4 The Role of Circulating circRNA in Esophageal Cancer

Esophageal cancer is the eighth most common cancers in the world and is widely considered to be a genetic disease with high incidence and high mortality in Asia [75]. Esophageal squamous cell carcinoma (ESCC) is one of the main subtypes and originates from esophageal epithelial cells [76,77]. In recent years, there have been many studies on circulating circRNA in ESCC. Recent studies have found that ESCC tissues can secrete circRNA into plasma. Patients with high plasma circ-SLC7A5 were associated with high tumor-node-metastasis (TNM) stage, and overall survival was often shorter than patients with high levels [77]. Hu et al. [78] suggested that plasma CIRCGSK3β expression could detect ESCC. The up-regulated expression of plasma circGSK3β was positively correlated with the late clinical stage and poor prognosis of ESCC patients [78]. Huang et al. [79] experimentally verified that the expression of plasma hsa_circ_0004771 was decreased in patients with ESCC after surgery. This finding suggests that the increase in plasma hsa_circ_0004771 may be related to the tumor [79]. Thus, we consider that plasma circRNAs as non-invasive biomarkers for ESCC and may provide diagnostic and prognostic value for it.

3.2.5 The Role of Circulating circRNA in Pancreatic Cancer

Pancreatic cancer is a malignant cancer of the digestive system, with insipid onset and rapid development, leading to delay and difficulty in early diagnosis and poor prognosis. 90% of pancreatic cancers are pancreatic ductal adenocarcinomas (PDAC) [80,81]. Currently, CA199 is a commonly used serum biomarker for PDAC [82]. In recent years, there have been some studies on the combined diagnosis of circulating circRNA and CA199 for pancreatic cancer. For example, the expression of circ-LDLRAD3 in serum samples of pancreatic cancer is higher than that of healthy volunteers, and circ-LDLRAD3 is associated with pancreatic cancers metastasis. Besides, the serum level of circ-LDLRAD3 is closely related to the level of blood CA199, and the combination of circ-6909D3 and CA199 can improve the diagnostic value [83]. By detecting the expression of circulating circRNA in PDAC patients, Shao et al. [84] found that their overexpression can increase the resistance of normal PANC-1 and PACA-2 cells to gemcitabine. It can be seen that circulating circRNA has diagnostic value for PDAC, and we hope that more studies will support this idea in the future.

3.3 Reproductive and Urinary System Cancers

3.3.1 The Role of Circulating circRNA in Breast Cancer

Breast cancer is a common cancer among women worldwide [85]. Although the treatment of breast cancer has made significant progress, its mortality rate is still high [86]. Early screening of breast cancer is very helpful for treatment and prognosis, and current studies have shown that the expression level of

plasma circRNA can reflect the progression of breast cancer. For example, cell-free RNA was used from the plasma samples of four breast cancers patients, and amplified qRT-PCR was used to detect circCNOT2. All samples showed detectable variable levels of circCNOT2, indicating that circRNAs in plasma [87]. CircRNAs can be used as biomarkers for breast cancer, and joint diagnosis can improve accuracy. For instance, the expressions of hsa_circ_0069094, hsa_circ_0079876, hsa_circ_0017650, and hsa_circ_0017536 in the plasma of patients with breast cancer were significantly higher than those of healthy controls. When combining hsa_circ_0069094 and hsa_circ_0017650, the AUC becomes 0.8469, and when combining all four circRNAs, the AUC is 0.8397 [86]. Furthermore, the diagnostic accuracy of hsa_circ_0001785 plasma was higher than CEA and cancer antigen-153 (CA153). The expression level of plasma hsa_circ_0001785 was closely related to histological grade, TNM stage and histological level, and its expression in plasma was significantly lower after surgery than before surgery [88]. The above researches have shown that plasma circRNA has great potential in the diagnosis of breast cancer.

3.3.2 The Role of Circulating circRNA in Ovarian Cancer

Ovarian cancer (OC) is one of the most common gynecological cancer in the world [89]. Although the surgical level has improved, the five-years survival rate is still not satisfactory [90]. CircRNAs have a long half-life in body fluids, so people are actively exploring circRNAs as biomarkers for OC diagnosis. A study found that 178 differentially expressed circRNAs were detected in the serum of OC patients, of which 175 were up-regulated and 3 were down-regulated and these circulating circRNAs may be related to the development of OC [91]. Circulating circRNAs may be valuable diagnostic biomarkers for early OC and have a potential role in disease progression. For example, circMAN1A2 is down-regulated in the ovary and can be used as a biomarker for ovarian cancer [47]. CircSETDB1 can be used as a new type of non-invasive biomarker to detect the progress of serous ovarian cancers (SOC) and predict the response of high-grade SOC to chemotherapy and relapse [92]. Hu et al. [90] found that circBNC2 is down-regulated in the plasma of epithelial ovarian cancers (EOC) patients, and they believed that circBNC2 may become a new biomarker for EOC. Thus, detecting the expression of circulating circRNA can predict the therapeutic effect of OC. We believe that circRNAs can be used as a biomarker for diagnosis and treatment of OC in the future.

3.3.3 The Role of Circulating circRNA in Prostate Cancer

Prostate cancer (PCa) is one of the leading cancers that cause death among men worldwide [93]. Currently, serum prostate-specific antigen (PSA) is still the standard biomarker for the diagnosis and treatment of PCa. However, PSA testing often leads to overdiagnosis and overtreatment due to its poor specificity [94]. It is proved that the expression of circZMIZ1 in the plasma of patients with PCa is higher than that in matched benign prostatic hyperplasia (BPH) patients. Thus, CircZMIZ1 can be considered as valuable biomarkers in PCa plasma [95]. Kong et al. [96] found that circFOXO3 is up-regulated in PCa tissues and serum samples, experiments have verified that circFOXO3 can be used as a promising biomarker for PCa. The combined diagnosis of circulating circRNA and PSA can be considered to make up for their shortcomings.

3.3.4 The Role of Circulating circRNA in Bladder Cancer

Bladder cancer is a common cancer of the male urinary system with high mortality [97]. Bladder cancer is classified as muscle-invasive bladder cancers (MIBC) and non-muscle invasive bladder cancer (NMBIC) [98]. CircRNAs can be detected in the serum of bladder cancer patients and is relatively stable. The levels of circFARSA, circSHKBP1, and circBANP in the serum of bladder cancer patients are significantly higher than those of healthy controls. Serum circFARSA and circBANP levels can be used as prognostic factors in patients with bladder cancer recurrence [99]. Compared with healthy controls, hsa_circ_000285 in serum is significantly reduced. Moreover, in patients with cisplatin-resistant bladder cancers, the

expression of hsa_circ_000285 is lower than that of patients who are sensitive to cisplatin [100]. Therefore, circulating circRNA can be used as a biomarker for the diagnosis of bladder cancers, and some can also reflect drug resistance, which is very helpful for treatment.

3.4 Blood System Cancer

3.4.1 The Role of Circulating circRNA in Leukemia

Leukemia is a malignant tumor of the blood system, which can be divided into acute leukemia and chronic leukemia. In recent years, it has been found that circRNA is involved in leukemia progression, so there are some studies exploring plasma or serum circRNA as biomarker. For instance, Circ-RPL15 in Chronic lymphocytic leukemia (CLL) plasma samples were significantly up-regulated, and ROC analysis showed that circ-RPL15 may be a potential biomarker for screening CLL [101]. The expression of circ_100053 in the serum was significantly higher than that of the healthy control group. The high expression of circ_100053 indicates a poor prognosis and imatinib resistance in patients with chronic myeloid leukemia (CML) [102]. We hope that more studies will explore the role of circulating circRNA in acute leukemia. From the above experimental studies, we believe that circulating circRNA can reflect the prognosis and resistance of CLL, which provides a new target for the future treatment of it.

3.4.2 The Role of Circulating circRNA in Multiple Myeloma

Multiple myeloma (MM) is a hematologic malignancy associated with plasma cells [103,104]. It is the second common hematologic malignancy with high recurrence rate and poor prognosis [105]. To search for potential diagnostic and therapeutic prognostic targets, Yu et al. [106] found that circ-MyBL2 was significantly reduced in MM tissue and serum samples compared to normal samples, and that its low level was associated with higher clinical staging, then speculated that serum circ-MyBL2 had good accuracy in the diagnosis of MM. We believe that circulating circRNAs, as diagnostic biomarkers of MM, have great potential in diagnosis and monitoring of prognosis.

3.4.3 The Role of Circulating circRNA in Lymphoma

Lymphoma include Hodgkin lymphoma and non-Hodgkin lymphoma. Diffused large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma in adults, accounting for about 30% of all cases [107,108]. It was found that plasma circAPC levels were significantly decreased in DLBCL patients compared with healthy controls, suggesting that circAPC is a new proliferation inhibitor, and restoration of its expression may be an effective treatment for DLBCL [109]. Circulating circRNA can be used as a biomarker of lymphoma, and it has clinical significance in treatment. However, there are few studies related to lymphoma at present, we believe that there can be more researches on treatment and prognosis in the future.

The above studies have confirmed the role of circulating circRNA in cancers of different systems. The main functions, sources and expressions have been summarized in Tab. 1.

Table 1: The role of circulating circRNAs in cancers

Function	circRNA ID	Cancers	Source	Expression	Reference
Diagnosis	hsa_circ_0005962	LUAD	Plasma	Up	[45]
	hsa_circ_0086414	LUAD	Plasma	Down	[45]
	hsa_circ_0013958	LUAD	Plasma	Up	[46]
	circMAN1A2	LUAD/NPC	Serum	Up	[47]

(Continued)

Table 1 (continued).

Function	circRNA ID	Cancers	Source	Expression	Reference
Diagnosis and prognosis	hsa_circ_0001715	LAUD	Plasma	Up	[48]
Treatment	circPVT1	LUAD	Serum	Up	[49]
Biomarker	circRNA_0000285	NPC	Serum	Up	[52]
Diagnosis	hsa_circ_0000520	GC	Plasma	Down	[57]
	hsa_circ_0021087	GC	Plasma	Down	[58]
	hsa_circ_0005051	GC	Plasma	Down	[58]
	hsa_circ_0006848	GC	Plasma	Up	[59]
Diagnosis and prognosis	hsa_circ_0027089	HCC	Plasma	Up	[64]
	hsa_circ_0003998	HCC	Plasma	Up	[65]
Prognosis	circRNA_101237	HCC	Serum	Up	[67]
Diagnosis	hsa_circ_0001445	HCC	Plasma	Down	[67]
	circVAPA	CRC	Plasma	Up	[72]
Prognosis	hsa_circ_0007534	CRC	Plasma	Up	[73]
Diagnosis	circ-ABCC1	CRC	Plasma	Up	[74]
	circ-CCDC66	CRC	Plasma	Up	[74]
	circ-STIL	CRC	Plasma	Up	[74]
Diagnosis	circ-GSK3β	ESCC	Plasma	Up	[78]
Diagnosis and prognosis	hsa_circ_0004771	ESCC	Plasma	Up	[79]
Prognosis	circ-SLC7A5	ESCC	Plasma	Up	[77]
Diagnosis	circ-LDLRAD3	PDAC	Serum	Up	[83]
Biomarker	hsa_circ_0069094	Breast cancer	Plasma	Up	[86]
	hsa_circ_0079876	Breast cancer	Plasma	Up	[86]
	hsa_circ_0017650	Breast cancer	Plasma	Up	[86]
	hsa_circ_0017536	Breast cancer	Plasma	Up	[86]
	circCNOT2	Breast cancer	Plasma	Up	[87]
	hsa_circ_0001785	Breast cancer	Plasma	Up	[88]
Diagnosis	circMAN1A2	OC	Serum	Down	[47]
Non-invasive biomarker	circSETDB1	OC	Serum	Up	[92]
	circBNC2	EOC	Plasma	Down	[90]
Biomarker	circZMIZ1	PCa	Plasma	Up	[95]
	circFOXO3	PCa	Serum	Up	[96]
Prognosis	circFARSA	Bladder cancer	Serum	Up	[99]
	circSHKBP1	Bladder cancer	Serum	Up	[99]
	circBANP	Bladder cancer	Serum	Up	[99]
Diagnosis and chemotherapy	hsa_circ_0000285	Bladder cancer	Serum	Down	[100]

(Continued)

Table 1 (continued).

Function	circRNA ID	Cancers	Source	Expression	Reference
Prognosis and resistance	circ_100053	CML	Serum	Up	[102]
Diagnosis and treatment	circ-RPL15	CLL	Plasma	Up	[101]
Diagnostic	circ-MyBL2	MM	Serum	Down	[106]
Diagnosis and treatment	circAPC	DLBCL	Plasma	Up	[109]

4 Conclusions

Based on previous studies on cancers biomarkers, circulating circRNAs were found as biomarkers for human cancers [110]. Current researches demonstrate that circRNA is rich in content, high in stability, and stable in peripheral blood [111]. Evidence has been that circRNAs expression in plasma or serum is associated with cancer progression, and a variety of circRNAs can be detected in blood samples collected from cancer patients [37]. Compared with other invasive tests, the method of detecting circRNAs by collecting patient blood is less harmful and more convenient, so circulating circRNAs can be used as noninvasive biomarkers for cancers.

Circulating circRNAs, mainly used to diagnose cancers, serves as biomarkers for monitoring cancer progression. Based on evidence drawn from the above studies, the expression level of circulating circRNAs also aids diagnosing cancers. Some authors believe that the combination of circulating circRNA and existing markers can improve the accuracy of detection. For example, Huang et al. believe that hsa_circ_0000745 plays an important role in GC. The combination of its plasma expression level and CEA level would provide a promising diagnostic marker for this malignant tumor [112]. In addition, circulating circRNAs can be utilized as dynamic indicators to monitor cancer progression. Circulating circRNAs are often expressed differently in cancer patients than in healthy controls, especially as the cancer progresses. CircRNAs can be conducive to treating cancers owe to its vital part in tumor genesis, proliferation, metastasis, invasion, stem cell regulation, and radiation resistance [113]. Statistical analysis prove that circulating circRNAs are related to the prognosis of cancers. The researches mentioned above have shown a correlation between circulating circRNAs and cancer prognosis, and their expression level can be detected to predict the prognosis of patients.

Circulating circRNA, with its biological functions, can be employed as biomarkers for diagnosis, treatment and prognosis of cancers. In addition, the detection of circulating circRNA levels in patients can be performed easily and cost-effectively with a non-invasive method. However, the researches of circulating circRNAs in cancers are far from enough since there lacks studies on the role of circulating circRNA in cancer treatment. If new progress and advances are made in treatment, the survival rate of patients should be better improved. There are many researches in the cancer of digestive system, but much fewer in other systems. Therefore, more experiments are still needed for verification. Through these existing studies, circulating circRNAs could be expected to serve as biomarkers for futuristic cancer diagnosis and treatment.

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