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Review

Role of circular RNAs in colorectal tumor microenvironment

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ABSTRACT

Circular RNAs (circRNAs) are a class of endogenous noncoding RNA, which were previously considered as a byproduct of RNA splicing error. Numerous studies have demonstrated the altered expression of circRNAs in organ tissues during pathological conditions and their involvements in disease pathogenesis and progression, including cancers. In colorectal cancer (CRC), multiple circRNAs have been identified and characterized as "oncogenic", given their involvements in the downregulation of tumor suppressor genes and induction of tumor initiation, progression, invasion, and metastasis. Additionally, other circRNAs have been identified in CRC and characterized as "tumor suppressive" based on their ability of inhibiting the expression of oncogenic genes and suppressing tumor growth and proliferation. circRNAs could serve as potential diagnostic and prognostic biomarkers, and therapeutic targets or vectors to be utilized in cancer therapies. This review briefly describes the dynamic changes of the tumor microenvironment inducing immunosuppression and tumorigenesis, and outlines the biogenesis and characteristics of circRNAs and recent findings indicating their roles and functions in the CRC tumor microenvironment. It also discusses strategies and technologies, which could be employed in the future to overcome current cancer therapy challenges associated with circRNAs.

1. Introduction

Colorectal cancer (CRC) is one of the most malignant tumors; the third commonly occurring and second leading cause of death globally after lung cancer [1]. The incidence and mortality rates of CRC are greatly affected by family history, age and lifestyle [2]. Even though surgical resection remains the best curative treatment strategy for early stage tumor, there is 30–60% chance for relapse which again increases the morbidity in CRC patients [3]. Despite of all the current advances in cancer therapies, their effectiveness in CRC patients is largely affected by the tumor immune microenvironment [4]. Mounting evidence suggest that multiple factors are involved in driving the onset and/or progression of CRC, including gene mutations, dysregulation in the chromosomal-copy number, atypical methylation profile, and post-transcriptional modifications, which can all lead to aberrant gene expression [5–9]. However, potential significant molecular mechanisms behind the development and progression of CRC are still elusive.

About four decades ago, the first reference of circular RNAs (circRNAs) was given as displaced loops of single stranded adenovirus DNA [10,11]. Later on, Nigro et al. reported the presence of some unexpected arrangements of exons, and called as "scrambled exons", while studying splicing in the tumor suppressor gene *DCC* (Deleted in colorectal cancer) [12]. Over the years, circRNAs were characterized as non-coding endogenous RNAs originated from alternate splicing and pre-mRNA processing of a large fraction of genes across eukaryotes ranging from fruit flies to human [13,14]. Following splicing and pre-mRNA processing, single stranded RNA forms circles by covalent binding and losing its poly A tail on 3′ end and 5′ caps [15]. Moreover, circRNAs have superior stability over linear isoforms, and they are conserved among a vast number of species including protists, nematodes and zebrafish [16], and abundantly expressed in cells, compared to the level of their linear counterparts [17]. However, reports showed that the abundance and localization of circRNAs within the cells vary across different cell types/conditions [18,19]. For instance, the predominant exonic forms of circRNAs leave the nuclei to reside in the cytoplasm, while the minor forms that contain introns reside in nuclei [20].

Multiple lines of evidence have indicated that circRNAs could interfere with the expression of genes to modulate cancer-related signaling pathways [21]. It has been shown that altered gene expression profiles are correlated with tumorigenesis in multiple cancer types and can contribute to different aspects of cancer progression [22]. Using

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Nomenclature

APC	Adenomatous polyposis coli
BCL2	B-cell lymphoma 2
CDK	Cyclin dependent kinase
CDRI	Cerebellar degeneration related protein 1
ceRNA	Competing endogenous RNA
circRNA	Circular RNA
ciRNA	Circular intronic RNA
CRC	Colorectal cancer
ecircRNA	Exonic circular RNA
EGF	epidermal growth factor
EGFR	Epidermal growth factor receptor
EIcircRNA	Exon-intron circRNA
EMT	Epithelial to mesenchymal transition
ERK	Extracellular signal-regulated kinase
HCC	Hepatocellular carcinoma
ICS	Inverted complementary repeats
IRES	Ribosome entry site (IRES)
m^6A	N6-methyl adenosine
MAPK	Mitogen-activated protein kinase
MDM2	Mouse double minute 2 homolog
MDSC	Myeloid derived suppressor cell
MREs	miRNA response elements
miRNA	Micro-RNA
ORF	Open reading frame
PD-1	Programmed cell death receptor-1
PD-L1	Programmed death ligand-1
PI3K	Phosphatidylinositol 3-kinase
PKB	Protein kinase B
Pre-mRNA	Premature messenger RNA
Pre-tRNA	Premature transfer RNA
TERT	Telomerase reverse transcriptase
Tiam1	T lymphoma invasion and metastasis protein 1
TME	Tumor microenvironment
TP53	Tumor protein P53
TSEN	tRNA splicing endonuclease
tricRNA	tRNA intronic circular
RBPs	RNA binding proteins
RNA Pol II	RNA polymerase II
Sry	Sex determining region Y
Tregs	T regulatory cells
VEGF-A	Vascular endothelial growth factor-A
ZEB1	Zinc finger E-box binding homeobox 1

high-throughput approaches, researchers have shown that circRNAs are differentially expressed in various malignancies, including CRC [23]. CircRNAs are stable, abundant, and can be easily detected and quantified in samples, such as blood, urine and saliva, which enable their potential use as ideal biomarkers for cancer diagnosis and prognosis [24].

The crosstalk between circRNAs and components of the tumor microenvironment (TME) is becoming a hot spot for the researchers in the cancer field. Deciphering such an interplay will help in establishing the role of circRNAs in cancer, and understanding their contribution to the development of resistance to cancer therapy [25]. The nature of the TME has a great influence on the invasiveness, metastatic potential of the tumor as well as the emergence of drug resistance in multiple cancer settings including CRC [26–28]. Further investigations on the involvement of circRNAs in the colorectal TME may provide plausible discovery of novel biomarkers and therapeutic targets in CRC patients [24]. Furthermore, targeting circRNAs in the colorectal TME may accomplish greater therapeutic efficacy than current therapeutic modalities.

2. The tumor microenvironment

The TME of solid tumors like CRC consists of multiple cell types, such as immune cells, tumor cells, endothelial and stromal cells, and creates a complex suppressive network enabling cell-to-cell interactions favoring tumor survival, growth and metastasis [27]. These dynamic interactions are crucial for the heterogeneity, clonal development, drug resistance and metastasis of malignant cells [27,29]. Tumor cells release various chemokines and cytokines to promote the trafficking of suppressive immune cells, such as myeloid-derived suppressive cells (MDSCs) and T regulatory cells, into the TME and induce the conversion of fibroblasts into cancer-associated fibroblasts (CAFs), which in turn support tumor growth and progression and suppress effector T cell function and proliferation [27,29].

The composition and nature of the TME can be modulated by multiple genetic, epigenetic, and metabolic factors, and immunosuppressive mechanisms acquired during the progression of cancer or upon therapeutic interventions [9,27,28]. Therefore, a deep understanding of the molecular, cellular, and metabolic characteristics of the TME is vital to reveal the underlying mechanisms driving such effects, and to determine the therapeutic outcomes in cancer patients [30]. Indeed, numerous therapeutic modalities fail to show clinical efficacy in targeting tumor cells due to the dynamic changes within the TME. This urges the need to perform further investigations to gain better understanding of the TME and pathological mechanisms, which can potentially further our understanding of immune regulation, identify diagnostic and prognostic/predictive biomarkers to ease the screening/diagnosis of cancers, predict disease outcomes in response to therapy and distinguish responders and non-responders. Additionally, more focused research can potentially identify candidates for novel therapeutic targets to improve clinical outcomes in cancer patients.

3. Classification and biogenesis of circular RNAs

Based on the composition of circRNAs, they are classified into four categories; (i) RNA circles transcribed from exon, termed as Exonic circRNAs (ecircRNAs) [17], (ii) one or more exons with flanking introns forms Exon-Intron circRNAs (EIcircRNAs) [19], (iii) circRNAs derived solely from intronic region of pre-mRNA are intronic circRNAs or ciRNAs [31] (iv) circRNAs formed from intron of pre-tRNA called transfer RNA (tRNA) intronic circular RNAs (tricRNAs) [32]. There are three models explaining the biogenesis of the dominant class exonic circRNAs in eukaryotes (Fig. 1); (i) lariat-driven circularization/exon skipping [33], (ii) intron-pairing driven circularization/back splicing [34], and (iii) RNA binding protein (RBP)-driven circularization [35].

In eukaryotes, canonical spliceosome removes introns from pre-mRNA and joins the exons to form linear mRNA of 5′ to 3′ polarity by a splicing reaction which can be summarized in two steps; (i) the 2′ OH group of adenosine residue at the branch point within the intron attracts nucleotide at 5′ splice site and forms a 2′–5′ phosphodiester bond to release the intron lariat, and (ii) the free 3′ OH group released upon 2′–5′ phosphodiester formation attracts 5′ splice site of downstream exon resulting in the joining of exons by a 3′–5′ phosphodiester bond [36]. In exon skipping model, the excised intron lariat containing one or more skipped exons proceeds to internal splicing giving rise to circRNAs [15]. Whereas in intron-pairing driven circularization, base pairing occurs between introns due to inverted repeats, followed by back splicing to join 3′ and 5′ splice sites resulting in the formation of circRNA. In both events, intron may or may not be retained to form either EIcircRNAs or ecircRNAs, respectively [13]. Instead of base pairing, RBPs also act as a bridge to shorten the distance between donor and recipient splice sites of

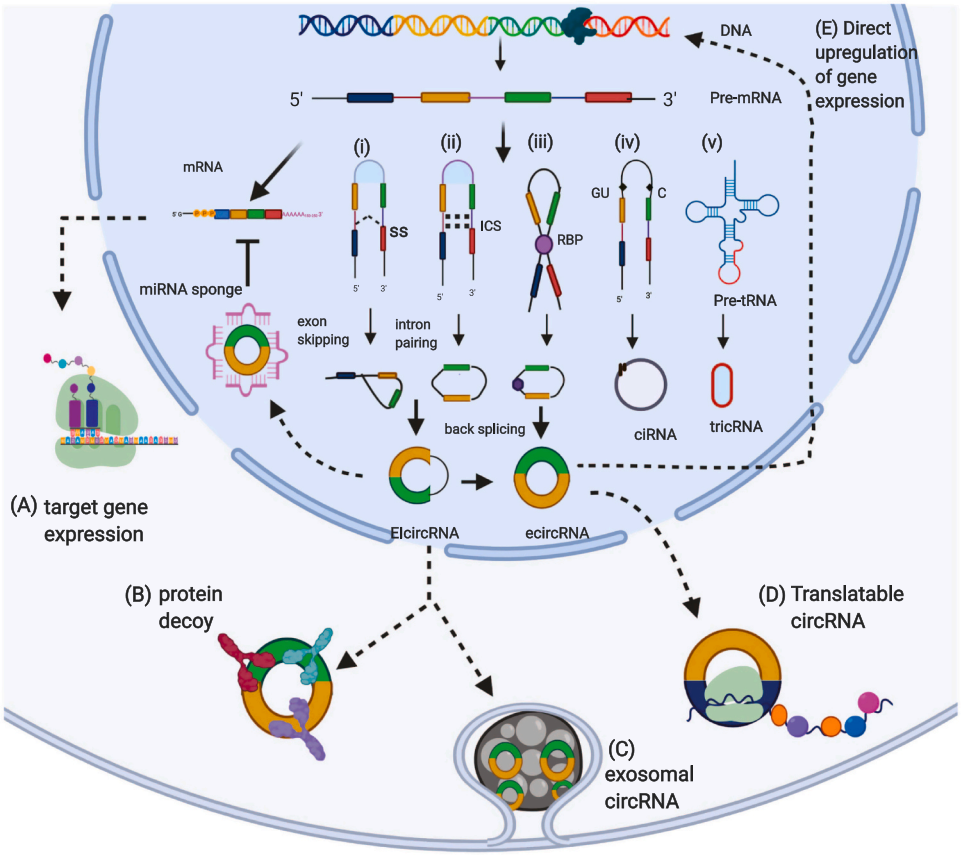

Fig. 1. Biogenesis of circRNA. (i) Lariat-driven circularization: during splicing, exon skipping results in the formation of lariat containing introns and exons, which further undergoes internal splicing to yield EIcircRNA. (ii) Intron-pairing driven circularization: the 3′ and 5′ splice sites are joined by base pairing between the inverted complementary repeats (ICS) present in intron followed by back splicing to give rise to EIcircRNA. (iii) RNA binding protein (RBP)-driven circularization: splice sites are brought close to each other by RBP and form ecircRNA or EIcircRNA. (iv) Circular intronic RNA (ciRNA) is formed by the direct ligation of GU rich and C rich elements on the introns. (v) Special tRNA splicing enzyme cleaves intronic region of pre-tRNA, which is later ligated by a 3′–5′ phosphodiester bond to form tricRNA. Functions of circRNA: (A) circRNA binds and removes target miRNA to modulate the expression of target gene. (B) circRNA acts as a protein decoy or protein scaffolder either to bring the proteins and their targets close together to enhance their interaction or facilitate their proteasomal degradation. (C) circRNA is transferred through exosomes to distant sites where it carries out its specific function. (D) circRNA also encodes for a protein product through cap-independent translation initiation mechanisms. (E) circRNA enhances the rate of transcription through the interaction with RNA pol II.

flanking introns, followed by back splicing to form ecircRNAs [35]. It has also been reported that ciRNAs are formed by the splicing reaction between the 11 nucleotide GU rich element at 5′ splice site and 7 nucleotide C rich element at 3′ branch point on the introns [31]. Notably, tRNA splicing endonuclease (TSEN) cleaves pre-tRNA at the splicing motif to release the tricRNAs by direct ligation [37].

The expression of circRNA is well-regulated and dependent on gene, cell, and tissue type [19]. At the gene level, circRNA biogenesis depends on the number and length of exons and introns and enrichment of splice sites [38]. Later, the expression of circRNA is regulated during gene transcription where pre-mRNA is formed. Of note, several *cis* and *trans* acting elements can control back splicing efficiency and the biogenesis of circRNAs [38]. In addition to this, the availability of several others factors like RBPs, spliceosomal proteins, and ICS can affect their biogenesis [39]. Altered expression of circRNAs affects several downstream pathways and finally leads to pathological conditions as it will be described in the sections below.

4. Functions of circular RNAs in cancer

CircRNAs regulate tumorigenesis and cancer progression through epigenetic modulation of gene expression by various mechanisms (Fig. 1). To begin, circRNAs act as competing endogenous RNAs (ceRNAs) which sponge microRNAs (miRNAs) and interfere with their functions leading to aberrant expression of their target genes [40,41] (Fig. 1A). The presence of miRNA response elements (MREs) was first identified in circRNA derived from *CDR1* (cerebellar degeneration-related protein 1) gene in brain cells, which has 70 miRNA binding sites and has been implicated in many carcinomas [42]. The circRNA homeodomain-interacting protein kinase 3 (circHIPK3) sponges many miRNAs related with progression of various malignancies including lung and ovarian cancers [43,44]. Alternatively, circRNAs can bind to proteins and negatively affect the expression of several oncogenes and tumor suppressor genes such as *MYC* proto-oncogene, *TP53* (tumor protein P53) and *BCL2* (B-cell lymphoma 2) [45]. For instance, the circRNA Zinc Finger with KRAB and SCAN Domains 1 (circZKSCAN1) competitively binds to RBP-FMRP (fragile X mental retardation protein) and inhibits cell proliferation in liver cancer [46]. Additionally, circRNAs can act as scaffolder by bringing the proteins and their targets closer to enhance their interaction (Fig. 1B). For instance, the circRNA Forkhead Box O3 (circFOXO3) can form a complex with p21 and CDK2 (cyclin dependent kinase 2), which retards cell survival and proliferation and induces apoptosis in several carcinomas and leukemias [47–49]. Besides this, circFOXO3 can interact with MDM2 (mouse double minute 2 homolog; also known as E3 ubiquitin-protein ligase) to facilitate ubiquitination and degradation of p53, which is a classical pathway in tumorigenesis [50,51]. However, the protein binding capacity of circRNAs depends on their unique tertiary structure and are more complex compared to linear RNAs [52]. Furthermore, circRNAs can be encapsulated in exosomes, which are small diameter vesicles originated from endosomes and formed from donor cells then fused into recipient cells [53,54]. This enables the transfer of exosomal circRNAs to distant sites where they exert tumor-promoting or tumor-suppressive functions [54] (Fig. 1C). Wang et al. demonstrated that exosomes derived from high metastatic hepatocellular carcinoma (HCC) cells are enriched with exosomal circPTGR1 (circRNA Prostaglandin Reductase 1), which can increase capacity of tumor cell migration and invasion and ultimately lead to the progression of HCC [55]. Additionally, exosomal circRNAs in body fluids, such as plasma, serum, urine, synovial fluid and cerebrospinal fluid, can also serve as diagnostic or prognostic biomarkers in cancer and can influence host anti-tumor immunity and response to cancer therapy [54]. For instance, Chen et al. reported that immunosuppression in metastatic melanoma patients is associated with high levels of circulating exosomal PD-L1 (programmed death ligand-1),

which can predict the response to anti-PD-1 (programmed cell death receptor-1) therapy [56].

Exonic circRNA present in the cytoplasm can also serves as templates to be translated into proteins through cap-independent translation initiation mechanism (Fig. 1D) as they contain internal ribosome entry site (IRES) and open reading frame (ORF) [57,58]. Studies have shown that the first identified protein coding circRNA in mouse myoblast, circZNF609, is translated in a cap independent manner using IRES [59,60]. Functions of circZNF609 include the facilitation of myogenesis and G1-S progression in rhabdomyosarcoma by upregulating cell-cycle related genes [61], and stimulation of cell proliferation and migration in several carcinoma including glioma, and gastric and breast cancers [62–64]. On the contrary, circZNF609 acts as a tumor suppressor in CRC by upregulating p53 and promoting apoptosis [65]. Currently, multiple circRNAs including circSHPRH, circAKT3, circβ-catenin, circLgr4, and circPPP1R12A encode proteins have been shown to involved in the regulation of cell proliferation, migration/invasiveness, and self-renewal in different cancer settings [66–70]. For instance, circSHPRH, encodes SHPRH-146aa protein and has been shown to inhibit malignancy and tumorigenesis through the ubiquitination of proliferating cell nuclear antigen (PCNA) in glioblastoma [66]. Notably, other findings have shown that a common base modification of N^6-methyladenosine (m^6A) in RNA is capable of driving protein translation of circRNAs in human [71]. For instance, expression profile analysis has shown that a large fraction of circRNAs with m^6A modification like circMART3 were translatable [71]. Finally, circRNAs act as *trans* acting elements to interact with several transcription factors and enzymes to enhance transcription [72]. For instance, circEIF3J and circPAIP2 present in the nucleus as EIcircRNAs can increase the transcription of the parental gene by interacting with RNA Pol II and transcription factors [73]. The interaction of circRNAs with transcription factors are depicted in Fig. 1E. Thus, the identification of circRNAs along with their downstream targets and their functions can further our understanding of the molecular and cellular mechanisms driving disease pathogenesis and progression, which could be of interest to develop new therapeutics and achieve favorable outcomes in cancer patients.

5. Expression and role of circRNAs in colorectal cancer

Transcriptomic profiling of circRNA indicates that several circRNAs are differentially expressed in tumor tissue, compared to normal tissue. For instance, circITGA7 is downregulated in CRC tumor tissues and cell lines, and it is involved in the suppression of cell proliferation and metastasis by inhibiting Ras pathway through increased expression of its host gene *ITGA7* [74]. Elevated expression of other tumor suppressive circRNAs such as circITCH, circDDX17, circFBXW7 and circCSE1L, have been also implicated in the suppression of cell proliferation and metastasis and were positively correlated with favorable prognosis in CRC patients [75–78]. Conversely, prominent circRNAs including circ_0000069, circ_0007843, circCCDC66, circHIPK3, circ_0020397 and circBANP are upregulated in colon cancer and promote the proliferation and migration of malignant cells [79–84]. The list of oncogenic and tumor suppressive circRNAs and their biological roles in CRC are summarized in Tables 1 and 2.

CircRNAs can potentially mediate stemness and metastasis in CRC through exosomes [85]. For instance, exosomes from $CD133^+$ cells carry circABCC1 and regulate CRC progression through activation of Wnt/β-catenin pathway [85]. Notably, the abundancy of circRNA is lower in colon cancer cell lines. This could be due to the distribution of circRNAs to daughter cells during the faster cell division [86]. Similarly, the abundancy and size of circRNAs were considerably inhibited in metastatic tumors, compared with primary tumors [87]. Exosomal circRNAs have also the potential for being diagnostic biomarkers to ease the screening and detection of CRC. For example, Pan et al. reported that serum exosomal circRNA, hsa-circ-0004771, is a novel diagnostic biomarker in CRC patients and its over-expression in the circulation of CRC patients is tumor-driven as evidenced by the downregulation of its expression in CRC patients post tumor resection [88]. Another study by Xie et al. identified serum exosomal circ-PNN (hsa_circ_0101802) as a potential diagnostic biomarker for CRC and suggested its possible involvement in CRC pathogenesis [89]. Additionally, a recent systematic meta-analyses on CRC patients indicated that the aberrant expression of circRNAs was closely associated with clinicopathological features and prognosis of CRC [90]. Altogether, these data underline the diagnostic and prognostic potential of circRNAs in CRC. Profiling patient samples

Table 1
Oncogenic circRNAs in colorectal cancer.

circRNA	Parent gene	Target miRNA	Biological effect	Reference
circBANP	BANP	p-Akt	Promotes cell proliferation	[84]
circACAP2	ACAP2	miR-21	Enhances tumor cell proliferation and invasion through the upregulation of *Tiam1* gene	[153]
circ_0020397	DOCK1	miR-138	Immune regulation	[83]
circHIPK3	HIPK3	miR-637	Drug resistance	[135]
		miR-7	Regulates cell growth and proliferation	[82]
circCCDC66	CCDC66	miR-33B/ miR-93	Proliferation, invasion, and metastasis	[154]
		miR-3140	Autophagy and tumorigenesis under hypoxia	[131]
circABCC1	ABCC1	miR-145	Stemness and metastasis Gene regulation	[85]
circ_100290		miR-516b	Activation of Wnt/ β-catenin pathway	[101]
ciRS-7	CDR1	miR-7	Activation of *EGFR* and *RAF1* oncogenes.	[104]
circMDM2	MDM2	P53	Cell cycle progression	[107]
circCTNNA1	CTNNA1	miR-149-5p	Upregulates *FOXM1* to promote tumor proliferation	[109]
circ_0001178		miR-382/ 587/616	Upregulates *ZEB1* to trigger EMT	[115]
circPTK2	PTK2		Promotes EMT by binding to vimentin on serine residue at 38, 55 and 82	[116]
circ_000984	CDK6	miR-106b	Tumorigenesis and progression	[155]
circPRKDC	PRKDC	miR-375	5-Fluorouracil Resistance inhibiting Wnt/β-catenin pathway	[156]
circ_001680		miR-340	Promotes chemoresistance through upregulating *BMI1*	[136]
circ_001971		miR-29c-3p	Induces angiogenesis through increasing *VEGFA* expression	[124]
circ_0136666		miR-136/ SH2B1	Cell cycle transition G0/ G1 phase	[157]
circ_0071589		miR-600/ EZH2	Cell viability, proliferation, invasion, and migration	[158]
circ_0136666		miR-136	*SH2B1* upregulation and cell cycle progression at G0/G1	[157]
circ_0000069	STIL		Mediates G0/G1 transition	[79]
circ_0000231		miR-502-5p	Upregulates Myosin VI and promotes glycolysis	[159]
circ_0007843		miR-518c-5p	Promotes invasion by upregulating matrix metallopeptidase 2 *(MMP2)*	[80]
circVAPA	VAPA	miR-101	Promotes proliferation, migration, invasion, and inhibits apoptosis	[117]

Table 2
Tumor suppressive circRNAs in colorectal cancer.

Circular RNA	Parent gene	Target miRNA	Biological function	Reference
circITCH	ITCH	miR-7	Inhibits Wnt/β-catenin pathway	[75]
circFBXW7	FBXW7		Upregulates expression of *NEK2* and *mTOR* and suppresses *PTEN* Expression.	[77]
circ_000523	METIL3	miR-31/ Dkk1	Inhibits EMT	[102]
circ_0001649	SHPRH		Contributes to pathological differentiation	[160]
circ_0007534	DDX42		Induces apoptosis	[161]
circDDX17	DDX17	miR-21-5p	Inhibits proliferation and induces apoptosis	[76]
circ_0060745	CSE1L	eIF4A3	Controls cell cycle-related factors (Cyclin D1, E1, CDK4)	[78]
circ_0014717			Upregulates cell cycle inhibitory protein p16	[108]
circ_0009361		miR-582	Upregulates *APC2* expression and inhibit Wnt/β-catenin pathway	[98]
circITGA7	ITGA7	miR-370-3p	Inhibits Ras signaling through suppressing neurofibromin 1	[74]
circ_103809	ZFR	miR-532-3p	Upregulates *FOXO4* expression	[162]
circ_0026344		miR-183	Represses EMT through Wnt/β-catenin pathway	[163]
circ_0137008		miR-338-5p	Inhibits EMT	[164]

to characterize and detect the expression of circRNAs and establish an array or panel to identify circRNA signature in CRC could be a promising approach for developing a non-invasive diagnostic method. Specifically, the detection of exosomal circRNAs in plasma can be utilized as a straightforward biomarker for diagnosing invasiveness and metastatic potential in CRC.

6. Functions of circRNAs in colorectal TME

6.1. CircRNAs in the regulation of genome mutations in CRC

As indicated in several studies, CRC tumorigenesis are closely linked to mutations in tumor suppressor genes (*TP53* and *APC*) and *KRAS* (oncogene) [91–94]. Progressive accumulation of these gene mutations is a key cause of malignancy in CRC [95]. Until now, the direct involvement of circRNAs in inducing mutations of these genes has not been confirmed; however, several circRNAs have been associated with the altered expression of these genes through epigenetic alterations induced by miRNA sponging. For instance, circZNF609 can induce apoptosis through the activation of *TP53* gene and suppressing CRC tumorigenesis [65]. A study by Dou et al. demonstrated that a global reduction in circRNAs is closely linked with *KRAS* mutation in HCT116 colon cancer cell line [96]. On the contrary, circ_100859 plays a key role in CRC development and has been positively associated with *KRAS* mutations [97]. Other studies showed that circRNAs, namely circ_009361 and circ-ITCH, inhibit tumorigenesis by upregulating *APC* expression [75,98]. On the other hand, Zhi et al. showed that a translatable circRNA, circLgr4, is elevated in colorectal tumors and colorectal cancer stem cells to inhibit *APC* expression and promote cancer stem cell renewal [69]. Further studies are required to confirm the role of circRNAs in the induction of genome mutations. Moreover, evaluating the nature of mutations induced by circRNAs can accelerate the development of novel screening methods for CRC detection.

6.2. Regulation of tumor growth and progression

circRNAs can modulate various signaling pathways and cellular events in the colorectal TME [21]. Key signaling pathways in cancer include mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK1/2), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB), also known as (AKT), and Wnt/β-catenin pathway [99]. Wnt/β-catenin signaling is the major signaling pathway implicated in the pathogenesis/progression and chemoresistance of CRC implicated by a mutation in the tumor suppressor gene *APC* (adenomatous polyposis coli) [100]. Fang et al. demonstrated that elevated levels of circRNA_100290 in CRC tumor tissues can activate Wnt/β-catenin pathway via miR-516b-*FZD4* axis, which is positively correlated with tumor progression and metastasis [101]. On the contrary, circITCH, arise from several exons of the gene encoding itchy E3 ubiquitin ligase, was downregulated in CRC tissues and has a predominant role in tumor suppression by sponging miR-7, miR-20a, and miR-214 to suppress Wnt/β-catenin pathway and ultimately inhibit the expression of *c-Myc* and *Cyclin-D1* genes [75]. It has been reported that circ_0000523 (also known as circ_006229) is downregulated in CRC cells leading to the activation of Wnt/β-catenin signaling and inhibition of apoptosis [102]. Additionally, prominent oncogene ciRS-7 is upregulated in CRC tissues, and its function was shown to inhibit epidermal growth factor receptor (EGFR) and RAF1/MAPK pathway, which is a novel therapeutic target in metastatic CRC [103,104].

The aberrant expression of circRNAs is paralleled with sustained cell proliferation which is one of the hallmarks of cancer [105]. circRNAs act as *cis* or *trans* acting elements and interact with transcription factors to enhance or repress the rate of parent gene expression. These gene products modulate signaling pathways and subsequently regulate cell cycle [106]. For instance, circMDM2 can promote proliferation of cancer cells by mediating G1/S transition through suppressing the expression of p53, which is responsible for inducing cell cycle arrest and apoptosis in response to DNA damage [107]. In contrast, circFOXO3 (another p53 regulator) acts as a tumor suppressor by binding to p21 and CDK2 and thereby halting cell cycle [51]. CircHIPK3 upregulates the expression of *EGFR* and *IGF1R* expression by sponging miR-7 in CRC, promoting tumor growth and metastasis [82]. circ_0014717 is downregulated in CRC tumor tissues and control tumor cell proliferation by inducing G0/G1 cell cycle arrest in vitro [108]. A novel circRNA from *CTNNA1* gene was identified as a regulator for DNA synthesis during S phase, and it facilitates G1/S transition to sustain proliferation in CRC [109]. Altogether, these reports demonstrate that circRNAs could regulate both initiation and termination of cell cycle in CRC. Although it is conclusive that circRNAs are key regulators of tumor cell proliferation in CRC, deeper understanding of the molecular pathways can lead to targeting the responsiveness of circRNAs to mitogens.

6.3. Induction of epithelial to mesenchymal transition, tumor invasion and metastasis

Epithelial to mesenchymal transition (EMT) is a key biological event associated with metastasis, in which epithelial cells become motile and attain mesenchymal nature by losing their polarity and anchorage [110], accompanied by reduced expression of cell junction proteins like E-cadherin and elevated expression of mesenchymal proteins like N-cadherin, fibronectin and vimentin [111]. In CRC, EMT is mostly activated by modulating signaling pathways including Wnt and Notch via transcription factors such as *ZEB1* (zinc finger E-box binding homeobox 1) and *SNAIL* [112,113]. Several circRNAs have been shown to act together with transcription factors and play regulatory roles in EMT [114]. For instance, circ_0009361 can suppress EMT by sponging miR-582 which regulates *APC2* expression and inhibit Wnt/β-catenin pathway in the colorectal TME [98]. Upregulated levels of circ_0001178 in CRC cells can activate EMT by upregulating the expression of the transcription factor, *ZEB1,* and sponging miR-382/587/616 which

subsequently increase N-cadherin expression [115]. Additionally, upregulated levels of circPTK2 (also known as circ_0005273) in CRC can modulate EMT by binding to phosphorylation sites on vimentin and enhance metastasis [116]. Another key regulator of EMT, circ_100290, has been shown to inhibit Wnt/β-catenin pathway through sponging miR-516b and downregulating *FZD4* expression [101].

Although the exact molecular mechanisms underlying circRNA contribution to tumor metastasis are not fully understood, it is evident that altered expression of circRNAs in CRC is associated with tumor invasiveness and distant metastasis. It has been reported that high expression of circITGA7 in CRC tissues inhibits metastasis through the downregulation of Ras signaling pathway and the binding to miR-370-3p [74]. On the other hand, Li et al. identified that circVAPA (circ_0006990) promotes invasiveness and inhibits apoptosis by binding with miR-101-3P [117]. A recent report by Zhang et al. revealed that a different regulatory axis of circVAPA acts as a molecular sponge for miR-125a to regulate the expression of *CREB5* and to promote CRC metastasis [118]. Additionally, circCCDC66, which is highly expressed in CRC polyp, can enhance anchorage-independent growth of cancer cells and act as an oncogene [81]. Another study reported that the upregulation of circHUEW1 is positively correlated with lympho-vascular invasion and advanced TNM staging [119]. Xu et al. indicated that circ_0001178 and circ_0000826 could be used as biomarkers to detect liver metastasis from CRC tumors [120]. To understand the underlying mechanisms of circRNA contribution to CRC tumor metastasis, deeper molecular investigations on tissue samples are required rather than comparative studies.

6.4. Induction of tumor angiogenesis

Angiogenesis is one of the important hallmarks of cancer and well-studied in metastatic CRC [121]. Several angiogenic inhibitors are currently used to treat metastatic CRC as they suppresses vascular development and tumor progression [122]. Some circRNAs were identified to regulate angiogenesis through modulating proangiogenic agents like epidermal growth factor (EGF) and vascular endothelial growth factor-A (VEGF-A) in different angiogenesis-related diseases [123]. In CRC, until now, only one circRNA was identified to modulate angiogenesis, circ_001971, which was shown to be upregulated in CRC tumor tissues and responsible for the upregulation of the proangiogenic factor VEGF-A through miR-29c-3p axis [124]. Additionally, it has been reported that cancer-derived exosomal miRNAs can promote the vascularization and angiogenesis in colon cancer [125]. Nonetheless, further investigations are required to explore more angiogenic-related circRNAs in CRC and the mechanistic axis of their regulation.

6.5. Induction of hypoxia

Hypoxia has always been studied in the context of cancer as it diverts the cellular energetics within the TME towards the survival and progression of cancer. Despite advocating malignancy, hypoxia even impedes the efficacy of cancer therapies including immunotherapy [126]. Mounting evidence suggests that crosstalk between hypoxia and circRNAs aggravates the pathophysiology in the colorectal TME [127,128]. For instance, circ-ERBIN (ERBB2 interacting protein or ERBB2IP) triggers enhanced expression of initiation factor 4E binding protein 1 (4EBP-1) via sponging of miR-125a-5p and miR-138-5p, which in turn activates the translation of the hypoxia inducing factor-1 alpha (HIF-1-α), a master gene regulator of hypoxia [129]. Dysregulation of HIF-1-α pathway ultimately promotes angiogenesis, EMT, and metastasis through direct regulation of ZEB1 in CRC [130]. Additionally, increased expression of oncogenic circRNA, circCCDC66, in hypoxia-induced CRC inhibited the expression of miR-3140 followed by enhanced autophagy to facilitate CRC progression [131]. Furthermore, hypoxia induces the upregulation of a prominent circRNA, circZNF292, independently of HIF-1-α. Besides, ZNF292 is a tumor suppressor gene and its overexpression promotes angiogenic sprouting in hypoxia-induced endothelial cells [132]. Moreover, frame shift mutations in ZNF292 have been reported in several carcinomas including CRC [132]. Finally, prolonged hypoxia increases the abundance of circRNA, circ-133, in exosomes derived from hypoxia-induced CRC cell lines including SW480 and HCT116 [133]. However, the regulatory mechanisms of hypoxia in circRNA biogenesis are still not evident. Additionally, further understanding of downstream effectors of circRNAs in hypoxic colorectal TME is warranted to develop novel therapeutic approaches, which could target hypoxia and circRNA in CRC.

6.6. Induction of tumor resistance to chemotherapy and radiotherapy

Besides controlling the progression and metastasis of CRC, circRNAs can be also involved in modulating the sensitivity of tumor cells to therapy. Abu et al. identified several circRNAs which are differentially expressed in chemo-resistant and chemo-sensitive HCT116 cell line [134]. Authors reported that circ_103306 and circ_32883, derived from *STAB1* (stabilin1) and *EML5* genes, were significantly upregulated in CRC cells and capable of inducing drug resistance and immunosuppression via the interaction with miR-370-3p and miR-130b [134]. Similarly, higher expression of circHIPK3 in CRC tumor tissues revealed that it sponges miR-637 to upregulate *STAT3* and activate *bcl2*/beclin1 signaling pathway to mediate resistance to oxaliplatin (chemotherapeutic agent) [135]. Another example is circ_001680, which induces irinotecan chemoresistance in CRC by sponging miR-340 and increasing the expression of *BMI1*, gene responsible for controlling cancer stemness [136]. CircCCDC66 (circ_0001313) has been reported to promote radiotherapy resistance in CRC by sponging miR-338-3P and suppressing the action of caspase-3 during radiation [137]. Apart from this, circCCDC66 mediates chemoresistance through PI3KK-mediated *DHX9* phosphorylation and is highly expressed during oxaliplatin treatment [81]. Furthermore, there are many exosomes-derived circRNAs that mediate chemoresistance in several cancers including CRC [53,138]. Transcriptomic analysis of exosomal circRNAs in folfox-resistant HCT cells identified several dysregulated circRNAs [139]. CircRNAs in exosomes can be easily transferred from donor to recipient cells where they modulate gene expression and protein function and confer chemoresistance on target cells [138]. For instance, circ_0005963, which is present in exosomes derived from oxaliplatin resistant cells can reduce drug sensitivity after being transferred to oxaliplatin sensitive cells [140].

6.7. Modulation of anti-tumor immunity

CircRNAs are also involved in the regulation of immune responses within the TME [141]. Wang et al. identified circ_100783 as being involved in the loss of CD28 during $CD8^+$ T cell ageing through phosphoprotein-associated functions [142]. Later, microarray analysis in bone marrow-derived macrophages (BMDMs) indicated the contribution of several circRNAs to macrophage differentiation and polarization [143]. Meanwhile, the role of circRNAs in anti-tumor immunity is more evident by the detection of circ_0020397 in CRC cells, and its characterization as a tumor-promoting or oncogenic circRNA, involved in tumor invasion and progression [83]. Furthermore, circ_0020397 is elevated in CRC cells and sponges miR-138 to promote the expression of its target genes, *TERT* (telomerase reverse transcriptase) and *PD-L1* [83]. Elevated expression of *TERT* gene supports cancer cells to bypass anti-growth signals and stimulate their proliferation [144], while PD-L1 surface protein binds to its receptor PD-1 present on T cells resulting in the suppression of T cell activation and anti-tumor immune responses [145], and cancer progression [146]. Additionally, it has been reported that increased protein levels of PD-L1 can be driven by the action of ciR7 in miRNA-independent fashion by modulating the expression of transmembrane proteins, CMTM4 and CMTM6 [147,148]. Alternatively, exosomes derived from CRC cells can induce differentiation of

peripheral blood CD4$^+$ T cells to T regulatory-like cells via the activation of TGF-β1/Smad signaling and suppressing SAPK signaling [149]. This implies that more studies are demanded in this field to uncover the role of circRNAs in immune evasion. However, various roles of circRNAs in the colorectal TME including cell signaling, epithelial to mesenchymal transition, angiogenesis, tumor metastasis, drug resistance and tumor immune evasion are briefly depicted in Fig. 2. Collectively, these findings suggesting the importance of identifying circRNAs that could serve as diagnostic or prognostic biomarkers for CRC and indicating the need to gain insights into the mechanistic roles of circRNAs within the colorectal TME which suppress anti-tumor immunity and promote tumorigenesis. This can be particularly helpful in advancing the screening of CRC and defining better therapeutic strategies to maximize clinical outcomes in CRC patients.

7. Conclusions and future perspectives

The involvement of oncogenic circRNAs in CRC invasion and metastasis has been well-studied and demonstrated using in vitro and preclinical models. Oncogenic circRNAs within the colorectal TME are capable of inducing cell cycle progression, stimulating signaling pathways which promote tumor cell proliferation/growth and EMT, and facilitating tumor resistance to chemotherapy and radiotherapy. However, further studies on the characterization of EMT-related circRNAs and identification of their mechanisms of action should provide better insights into potential treatment strategies for metastatic CRC. Alternatively, it is important to note that each oncogenic circRNA can have one or multiple target miRNA(s) and/or linear mRNA(s) to alter their expressions and exert a tumorigenic function. Therefore, targeting oncogenic circRNAs should be performed carefully taking the target miRNA and linear mRNA into considerations which is affected upon the inhibition of particular circRNA(s) [45]. Additionally, few circRNAs have been identified to take part in mediating immune evasion and angiogenesis. However, more studies are required to uncover more circRNAs (oncogenic or tumor suppressive), their functions and mechanisms of action in the colorectal TME. For instance, their effects on immune cells such as T cells, B cells, NK cells, MDSCs, macrophages and granulocytes should be defined, which has been already proven in other carcinomas. Moreover, circRNAs could serve as potential diagnostic or prognostic cancer biomarkers; however, further validation studies in

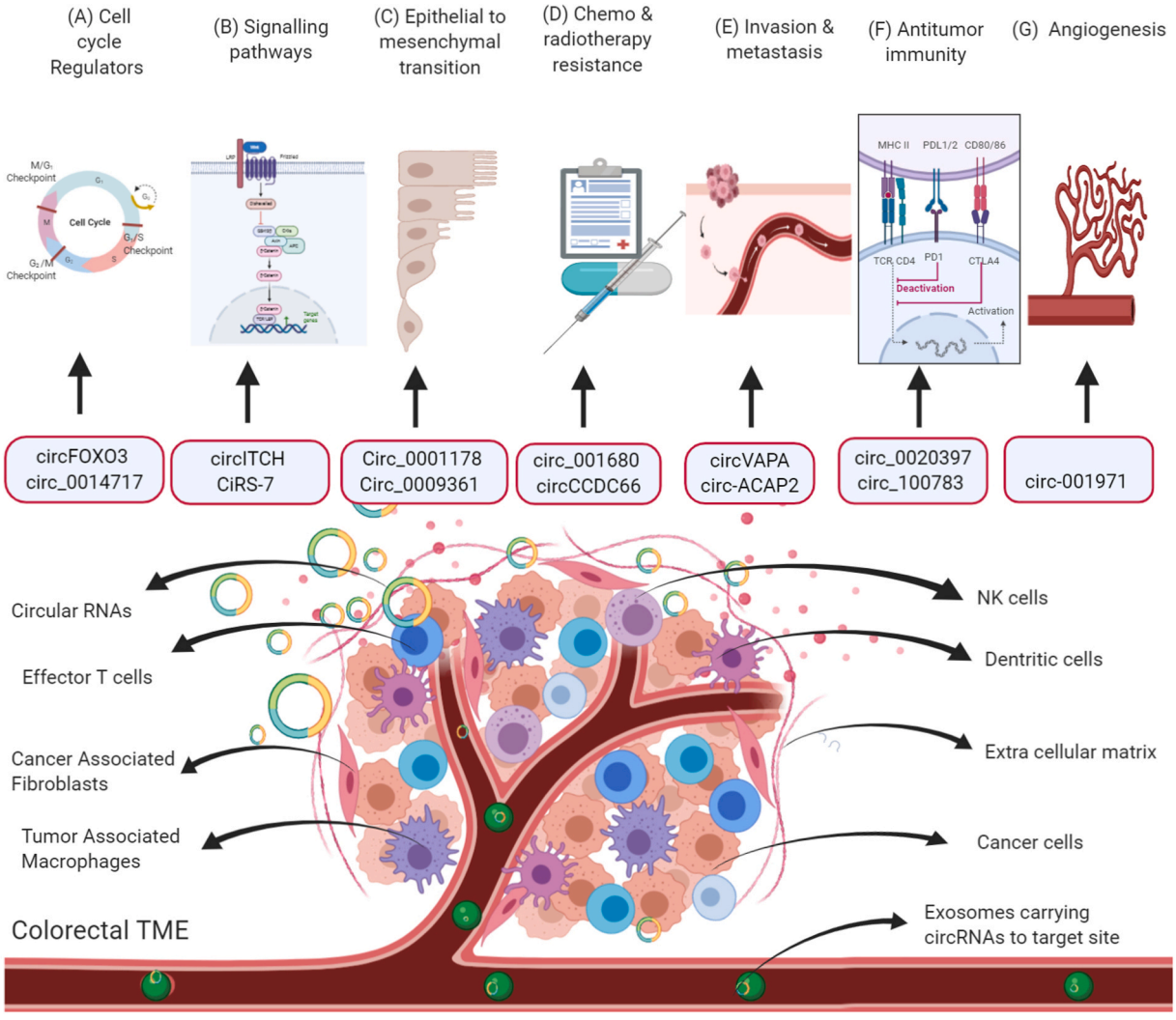

Fig. 2. CircRNAs in the tumor microenvironment of colorectal cancer. (A) circFOXO3 and circ_0014717 suppress tumor cell proliferation by inducing cell cycle arrest. (B) circITCH inhibits Wnt/β-catenin pathway, while ciRS-7 inhibits EGFR/MAPK pathway leading to the suppression of tumor growth. (C) circ_001178 induces EMT through *ZEB1*, while circ_0009361 inhibits EMT by regulating *APC2* expression. (D) circ_001680 mediates resistance to chemo drug, irinotecan, via upregulating *BMI1* gene and circCCDC66 induces resistance to radiotherapy by suppressing caspase-3 activity. (E) CircVAPA and circACAP2 promote tumor invasion and metastasis through sponging miR-101 and miR-21, respectively. (F) circ_0020397 promotes immune evasion by increasing the expression of *PD-L1* and *TERT* genes, while circ_100783 facilitates T cell ageing. (G) circ_001971 induces tumor angiogenesis by upregulating the gene expression of the proangiogenic factor VEGF-A.

large patient cohorts and examining their long-term follow-up clinical information [21,150].

Deeper insights into the functions of exosomal circRNAs in CRC are also required to further understand how they can mediate chemo-resistance and convert effector T cells to Tregs within the TME. Up to date, majority of studies have reported the involvement of circRNAs in tumorigenesis through miRNA-mRNA transcriptional regulatory axis, while their functions after being translated into proteins have not been explored. The introduction of circRNA as promising cancer therapeutic agents could be advantageous given their stability and capacity of "sponging" miRNAs and proteins. However, additional investigations are required for the identification and characterization of more translatable circRNAs, and their potential to encode tumor suppressor proteins as a therapeutic strategy for cancer in the future.

Although the scope of circRNAs in the field of translational medicine is getting widened, all these gaps of knowledge must be filled to provide novel insights into the role of circRNAs in CRC development and progression. Developing feasible therapeutic strategies to target oncogenic circRNAs include designing of exogenous siRNAs which complement target sites within the corresponding circRNAs. Alternatively, gene therapy could be employed to enhance the expression of tumor-suppressor circRNAs [31,151]. circRNAs could be directly applied into therapeutic regimens; however, extra cautions should be taken not to trigger immune-related adverse effects following the application of foreign circRNA [152].

CRediT authorship contribution statement

Jasni Viralippurath Ashraf: Writing - original draft. **Varun Sasidharan Nair:** Writing - review & editing. **Reem Saleh:** Writing - review & editing. **Eyad Elkord:** Supervision, Writing - review & editing.

Conflict of interest statement

The authors declare no conflicts of interest.

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