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Original Article

CircRNAs as promising biomarkers of inflammatory bowel disease and its associated-colorectal cancer

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Abstract: In recent years, research on the pathogenesis of inflammatory bowel disease (IBD) and its associated-colorectal cancer has been well documented to involve environmental, genetic, immune, and intestinal microbiota factors. Evidence indicates that, regardless of the current high global incidence of IBD with over 3.5 million cases in Europe and North America only, it continues to emerge in newly industrialized countries across Asia, Middle East, and South America. Individuals with IBD have significant increased risk of gastrointestinal and extra-intestinal malignancies, particularly, colorectal cancer (CRC) and lymphomas. Among the significant areas of exploration in IBD and its associated-CRC is the search for effective and reliable diagnostic and prognostic markers, and treatment targets. To this effect, the role of non-coding RNAs in IBD and its associated-CRC has attracted research attention, among which microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) get more detailed exploration while little is known about circular RNAs (circRNAs). This review focuses on the emerging role of circRNAs in the diagnosis, prognosis, and treatment of IBD and its associated-CRC. It introduces the biogenesis of circRNAs and brings an up-to-date report on those found within IBD and CRC environment, as well as their participation toward the promotion or suppression of the conditions, and their diagnostic potentials.

Keywords: Circular RNA, inflammatory bowel disease, colorectal cancer, biomarker, diagnosis, prognosis

Introduction

Inflammatory bowel disease (IBD), which mainly includes Crohn's disease (CD) and ulcerative colitis (UC), represents one class of idiopathic intestinal inflammatory autoimmune diseases involving the ileum, rectum, and colon [1, 2]. CD, also known as granulomatous enteritis, is chronic, regional and segmental, not only damaging the colon or terminal ileum but can also be discontinuous in any part of the gastrointestinal tract [3]. As a type of persistent diseases, CD often occurs accompanied by abdominal pain, diarrhea, fistula and intestinal obstruction. On the other hand, UC, only affecting rectum and colon, is a superficial inflammation characterized by bloody diarrhea [4, 5]. Multiple factors participate in the formation and development of IBD including immune-modulation, genetic susceptibility, environmental factors and gastrointestinal microbiota [6, 7]. Furthermore, IBD has a high potential of progressing into colorectal cancer (CRC), referred to as colitis-associated colorectal cancer (CAC) according to many researchers [8, 9]. In recent years, there is an increasing incidence of IBD and CRC [10], but the exact mechanisms remain unclear. The available traditional treatments and diagnostic approaches have not yielded desired results, and this creates avenue for more effective therapeutic and diagnostic programs and research.

Circular RNAs (circRNAs), which were first observed under an electron microscope in the 1970s, belong to non-coding RNA lacking terminal structures of a 5'cap or a 3'polyadenylation [poly-(A)] tail [11]. On the basis of their locations, circRNAs can be generally classified as exon circRNAs (ecircRNAs), intron circRNAs (ciRNAs), exon and intron circRNAs (EIciRNAs), intergenic circRNAs and fusion circRNAs (f-circRNAs) [12]. In recent studies, circRNAs have attracted much attention due to their specificity

in tissues across diseases as well as their high stability and conservativeness. CircRNAs are proven to function as sponges for many special miRNA in chronic inflammation and cancers. For instance, the circular RNA circMAST1 was reported to promote hepatocellular carcinoma cell proliferation and migration by sponging miR-1299 [13], and oncogenic circular RNA Hsa-circ-000684 interacted with microRNA-186 in gastric cancer [14]. Moreover, circRNAs play significant roles in regulating RNA binding proteins (RBPs) and gene transcription [15, 16]. However, the specific roles of circRNAs in IBD and CRC are not clearly explored so far.

In this review, we explored the interaction between IBD, CRC and circRNAs. In addition, we discussed the emerging roles of circRNAs in the diagnosis, treatment and prognosis of IBD and its associated-CRC.

Inflammatory bowel disease

As a non-specific intestinal inflammatory disease, IBD, affecting the quality of life and family happiness of millions of individuals over the world, is faced with great challenge in diagnosis and treatment partly due to its uncertain etiology. CD, also called terminal ileitis, named after the first author “Crohn”, is a segmental and asymmetric IBD, mostly occurring at the end of the ileum. It used to be mistaken for “intestinal tuberculosis” due to the non-specific granuloma in pathology. Another kind of IBD, UC, affecting the rectum, has a feature of diffusion. Compared to CD, it possesses a higher incidence rate and affects more men than women. Despite the explicit differences in the pathological mechanisms of these two disorders, they are sometimes analogous in pathological features.

Bacterial infections, including imbalance of probiotics, and pathogenic bacteria are regarded as key factors that contribute to IBD. This has raised a number of research questions and related investigations in this area to establish the link. Wang and colleagues detected differences in the intestinal flora of IBD patients compared with normal controls through metagenomic analysis in colonic biopsy samples [17]. In a study focused on children with UC and CD, the authors indicated different expression of enteric virome and bacterial microbiota, which capably provided a promising link to IBD pathogenesis and diagnosis [18]. In a recent research, *Faecalibacterium prausnitzii phylogroups* were demonstrated to combine with *Escherichia coli* to offer a possible biomarker for differentiating the subtypes of IBD as well as CRC [19]. Various foods elements have also been implicated in the cause and progress of IBD, making eating habits an inevitable contributing factor in the pathogenesis of IBD. Grosse and colleagues showed that a plant-based diet has a positive effect on the occurrence and recovery of IBD patients [20]. After randomly giving a low-fat, high-fiber diet (LFD) and an improved standard American diet (iSAD--including higher quantities of fruits, vegetables, and fiber than a typical SAD) to UC patients, Fritsch and colleagues found that LFD reduced inflammatory markers (amyloid A, C-reactive protein) and intestinal pathogenic bacteria (*Actinobacteria*) in fecal samples [21], which is consistent with previous studies. On the contrary, the influence of smoking on CD and UC differs in each condition. It is reported that, while smoking may relieve UC, it rather promotes CD [22, 23].

Immune disorder mainly related to immune cells, adhesion molecules and cytokines, is seemingly the most basic associated pathogenesis of IBD. Immune cells such as T cells (Th17 cells in particular), macrophages, and dendritic cells (DCs), have been discussed extensively in relation to their complicated functions in inflammation [24, 25]. **Figure 1** illustrates the progress of intestinal inflammation with regard to these cells. A recent study applied single-cell analysis to determine the mechanisms of mucosal dysregulation in patients with IBD and to establish the differences in inflammatory responses in patients with UC and CD. Results showed increased HLA-DR^+CD38^+ T cells, $CXCR3^+$ plasmablasts, $IL1\beta^+$ macrophages and monocytes in IBD, and differential expression between CD and UC [26]. NF-κB and JAK-STAT signaling pathway, along with other related multiple immune molecules especially ILs, TNF, and VCAM were considered complex factors that participate in the process of IBD onset and progression. A study on extra-intestinal manifestations (EIMs) of the eyes in IBD patients reported that, mucosal address in cell adhesion molecule 1 (MAdCAM-1) was upregulated in retinal microvessels, and recruited gut-homing $CD4^+$ T cells to be co-localized with bipolar and ganglion cells during colitis

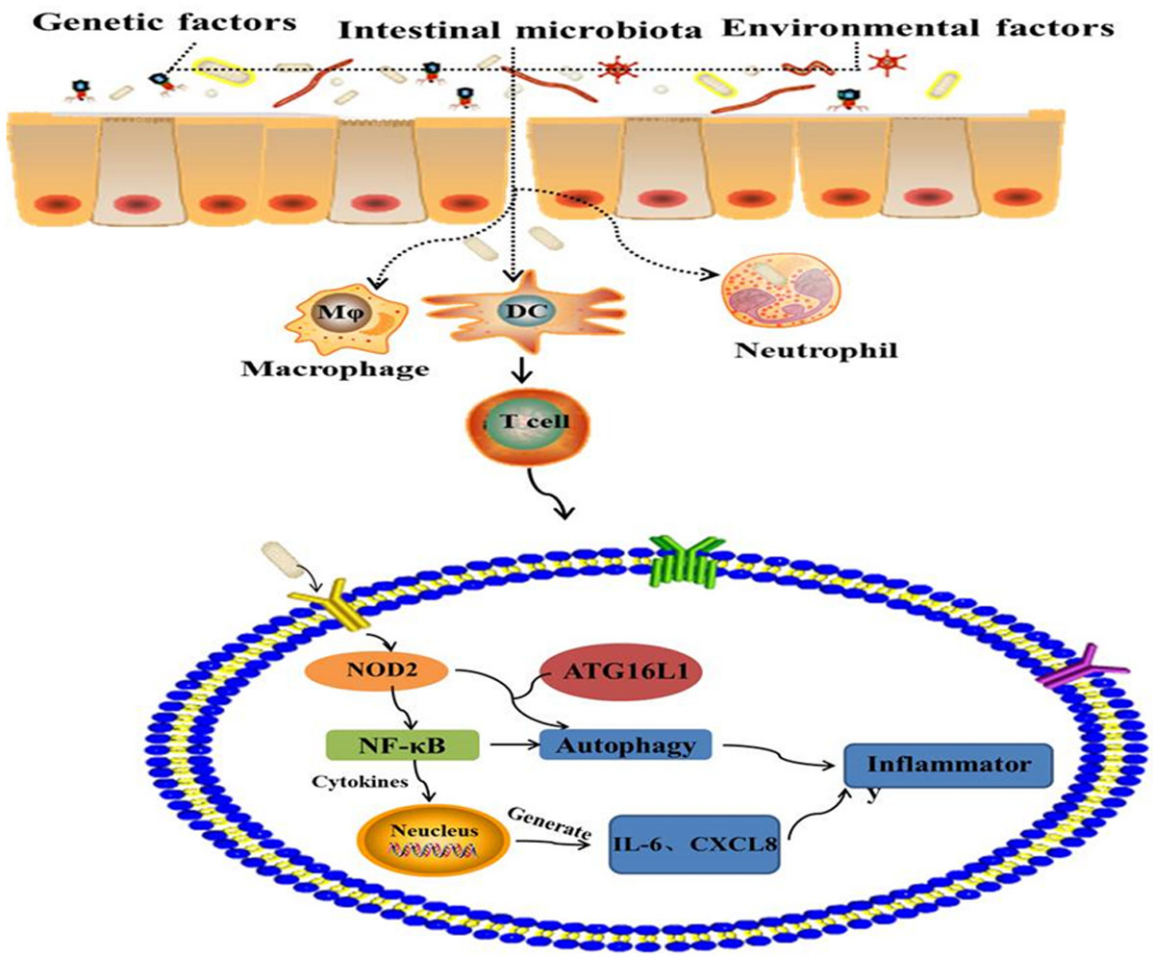

Figure 1. The course of intestinal inflammation: Under multiple influences of genetic factors, environment factors, and intestinal microbiota among others, the intestinal mucosal barrier is damaged, leading to bacteria invasion, and subsequently triggering a series of inflammatory reactions.

[27]. This offers a novel insight into the pathogenesis of IBD although further researches are needed. Moreover, genetics elements including mRNAs and mircoRNAs, have been shown to interact with other inflammatory factors to trigger the unset or progress of IBD.

Over the past few decades, an increasing number of researches on the etiology of IBD have been carried out in the exploration of the important role of genetic factors in the course of IBD. Researchers have mainly relied on the rapid development of genome-wide association studies (GWAS), next-generation sequencing and other gene detection technologies. GWAS identified a number of common genetic variants associated with more than 80 diseases and traits including IBD by analyzing numerous single nucleotide polymorphisms (SNPs) between different individuals [28]. It has been reported that GWAS has identified more than 200 non-overlapping risk loci for IBD [29], of which about 30 are shared between CD and UC [30]. To date, the systematic identification of IBD susceptibility genes has mainly concentrated on CD, while little is known in UC [31].

Nucleotide Binding Oligomerization Domain Containing 2 (NOD2), Autophagy-related protein 16 like 1 (ATG16L1), Immunity Related GTPase M (IRGM), interleukin 23 receptor (IL23R), Caspase recruitment domain-containing protein 9 (CARD9), Interleukin 18 receptor accessory protein (IL18RAP), Cullin 2 (CUL2), and other genes have been clearly studied as risk sites of CD. Studies have found that CD's susceptibility locus is located on chromosome 16 [32], and the first CD susceptibility gene, NOD2, was found in 2000 [33]. The leucine-rich repeat region of NOD2 has an inhibitory

effect on its activatable NF-κB pathway. At the same time, NOD2 is also an intracellular receptor for microbial pathogen components. When NOD2 site mutation causes structural changes in the leucine-rich repeat region or adjacent regions, it leads to the activation of the NF-κB pathway and increases the binding of intestinal bacteria and epithelial cells, causing inflammation. Momozawa and colleagues [34] found that IL23R has a low-frequency coding variant that has a protective effect in IBD. The CARD9 gene is a sensitive gene against microorganisms and the deletion of this gene blocks the metabolism of tryptophan by the flora and aggravate colitis. Some researchers have demonstrated its strong protective effect on the colon through experiments such as the mutation of the splice site of the CARD9 gene. CARD9 has been identified as associated with both CD and UC risk. In other genetic studies, researchers have reported Asn852Ser and Met863Val rare risk variants as more common in CD of Ashkenazi Jewish individuals [35].

Autophagy, a catabolic process that maintains intracellular homeostasis under stress, also plays an indispensable role in IBD. Studies on models and human clinical studies have shown that autophagy plays a crucial role in maintaining intestinal homeostasis and intestinal immune response. Genetic variants of several genes involved in this pathway including ATG16L1, Leucine-rich repeat kinase 2 (LRRK2) and IRGM, have been identified as risk related genes for IBD [36]. Mutations in ATG16L1, which is associated with autophagy, can cause structural changes in Paneth cells in the small intestine that will alter transcription factors and eventually lead to inflammation.

With UC, there are few studies on its susceptibility sites. Scholars have found that Interleukin-10 (IL-10) deficiency is at the core of the pathogenesis of UC, and the sequence variation of IL-10, Actin-related protein 2 (ARP2) and multiple other gene loci is conducive for the susceptibility to UC [31].

The conventional drugs of IBD including 5 aminosalicylic acid, glucocorticoid and immunesuppressants are still the predominant treatment methods even though biotherapy has moved to the clinic [37]. In recent years, significantly increasing IBD cases are being reported in the world, a clear indication of the need to understand its mechanisms and obtain ideal therapy for treatment.

Colorectal cancer

Colorectal cancer (CRC) is a common malignant tumor ranked second in gastrointestinal cancers that often occurs in the rectum and the junction of the rectum and sigmoid colon, severely affecting people's lives. Chronic inflammation and poor prognosis aggravate IBD, leading to alterations in free radicals, cytokines, adhesion molecules, and other factors that induce epithelial dysplasia and activate oncogenes, resulting in the development of IBD associated-CRC [38, 39]. Patients with IBD have been reported to suffer from CRC 1.5~2.0 times higher than the general population, whereas patients of CAC only account for 2% of all CRC cases [40]. Fujita and colleagues inferred that Interferon regulatory factor 1 (IRF1), a transcription factor that responds to Interferon gamma (IFN-γ) and Tumor necrosis factor alpha (TNF-α) [41], alters differently in human with IBD and CAC, suggesting that it may stimulate the onset of IBD and likely participate in its progression to CAC [42]. Additionally, KRAS, P53, APC genes, DNA mismatch repair gene (MMR) and other genes, which play critical roles in the pathogenesis of CAC, are intensely explored [43, 44]. Compared with IBD, TP53 and KRAS mutations are more common in CAC, while IBD patients with TP53 mutations are more susceptible to CAC [45]. Moreover, available evidence has highlighted that miRNAs as part of ncRNAs, promote CAC development, followed by a reduced expression of miR301A in IBD and CAC [46]. This calls for investigations into the intricate mechanisms underlying the progress of IBD to CRC.

Biogenesis and functions of circRNAs

In the past few years, noncoding RNAs (ncRNAs) accounting for ~90% of RNAs have attracted more attention due to their pivotal functions in a number of diseases especially cancers, among which miRNAs and lncRNAs get more detailed demonstration while little is known about circRNAs. CircRNAs are a class of non-coding RNAs originated from pre-mRNAs by back-splicing, resulting in covalently linked closed-loop structures with neither 5'caps nor 3'polarity [47, 48]. In this condition, there exist remarkable advantages in stability and resistance in

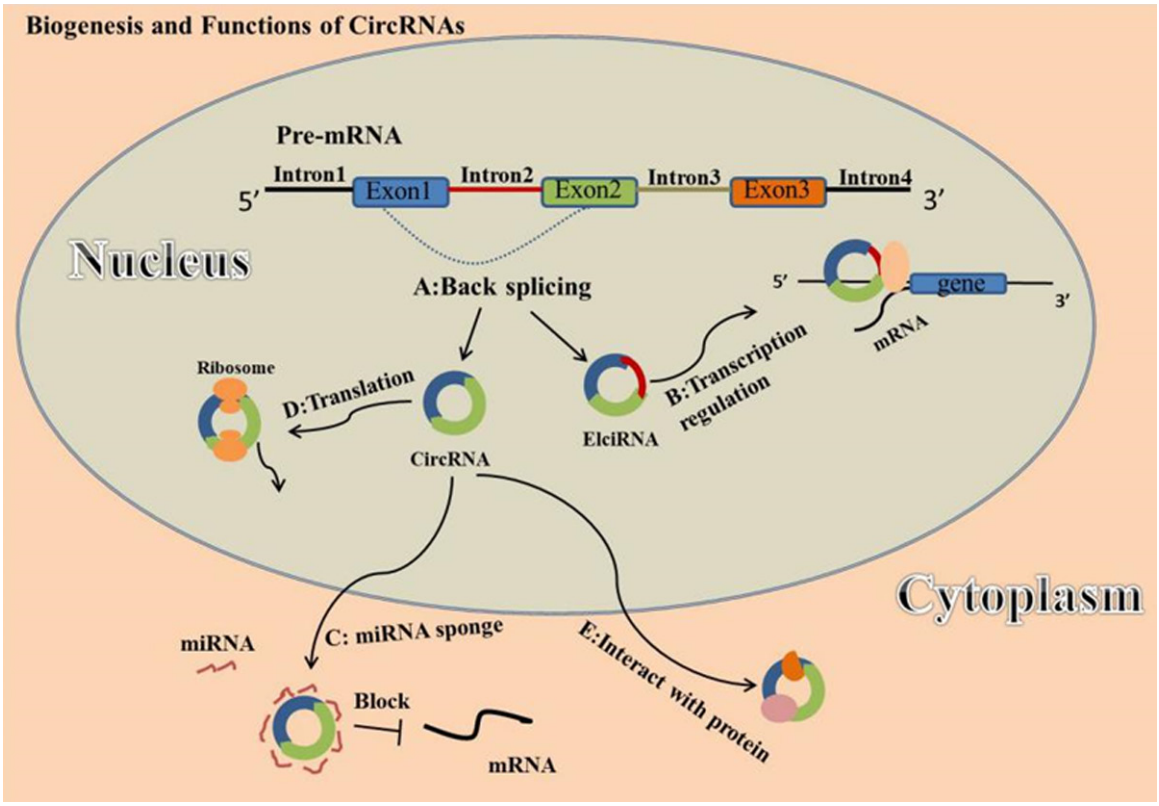

Figure 2. Biogenesis and Functions of CircRNAs. A: Back splicing. Its biogenesis is derived from pre-mRNA via back splicing. B: Transcription regulation. It binds to RNA Pol II in the promoter region to regulate transcription. C: miRNAs sponge. Inhibit the binding with corresponding mRNA by sponging miRNAs. D: Protein translation template. Some circRNAs can be translated into proteins. E: Interact with protein. The two combine to form complexes that regulate the expression and function of specific proteins.

circRNAs compared to linear RNAs. Most circRNAs are composed of exon sequences of protein-coding genes and are highly expressed in cytoplasm within eukaryotes, although some are generated from intronic, intergenic, or untranslated regions [49]. CircRNAs circularization is widely accepted by two classical models: lariat-driven circularization of only exons and intron-pairing-driven circularization between exons and introns [50]. Furthermore, circRNAs stemming from other regions such us 3'UTR and 5'UTR have also been reported [51] (**Figure 2**). Recently, a growing number of circRNAs are being identified with advanced high-throughput sequencing technologies, and by bioinformatics, which show multiple functions of circRNAs in many pathways and biological processes. MicroRNAs (miRNAs) with a length of 20 to 25 nucleotides are assumed to recognize and target mRNAs, contributing to their altered activities [52]. It is well-known that circRNAs could serve as miRNAs sponge by competitively binding with miRNAs response elements to form competing endogenous RNAs (ceRNA) networks to mediate their expressions. MiR-136, located in chromosome 14 has been identified to possess binding sites for several circRNAs. During an osteoarthritis study, a total of 71 differentially expressed circRNAs were detected and then validated to regulate MMP13 expression by competing for miR-136, which can be taken as a potential maker in osteoarthritis therapy [53]. About two years later, another study showed that hsa_circ_0023404 upregulates TFCP2 expression by sponging miR-136 in cervical cancer, and another group of researchers indicated that hsa_circ_013-6666 promoted the process of CRC development in a miR-136 related pathway [54, 55]. In addition, it has recently been reported that circRNA_100876 can sponge miR-136 to promote proliferation and metastasis of gastric cancer and osteosarcoma [56, 57]. Interestingly, an engineered circRNA with more than one binding sites, was found to inhibit both miR-132 and miR-212 activities to attenuate

pressure overload-induced cardiac hypertrophy [58]. The sponge functions of circRNAs exert indispensable roles in exploring their potential mechanisms.

Again, circRNAs can regulate RBPs that are essential for gene expression at post-transcription and further to have impact on their related mRNAs [59]. The ubiquitous RNA-binding protein human antigen R (HuR), also known as ELAV-like protein 1 (Elavl1), has previously been documented to interact with numerous mRNAs as well as several ncRNAs mainly microRNAs and lncRNAs [60, 61]. Likewise, the connections between circRNAs and HuR have also been investigated. Abdelmohsen and colleagues verified in a series of experiments and analyses that, circPABPN1 has a strong capacity to bind HuR, thereby inhibiting its combination with PABPN1 mRNA [62]. Moreover, preliminary work elucidated that certain circRNAs possess the ability of translating into proteins such as green fluorescent protein (GFP) with the support of N^6-methyladenosine (m^6A) found to augment mRNA translation efficiency [63, 64]. **Figure 2** illustrates the biological functions of circRNAs in summary.

CircRNAs in IBD and its associated-CRC

With the increasing popularity of circRNAs, they have recently been shown to possess great benefits for a number of diseases such as IBD [65], CRC [66], lung cancer [67], and osteoarthritis [68] although the exact mechanisms involved in their contribution are not well understood. Currently, IBD and its associated-CRC are still lacking ideal approaches in diagnosis and treatment. The mechanisms of other ncRNAs like miRNAs and lncRNAs are also being investigated [69-71], showing promising results. Here we make a summary of results of differentially expressed circRNAs that have been detected and confirmed in IBD and its associated-CRC.

A study showed that 163 circRNAs were highly expressed as against 55 circRNAs downregulated in three CD patients compared with healthy controls [72]. From 60 biopsies collected from 30 UC patients with inflamed and non-inflamed colon mucosa, a total of 264 circRNAs including 111 elevated and 153 downregulated circRNAs at different levels were recovered [73]. Microarray analysis identified 384 distinct circRNAs among five pairs RNAs samples between CD and healthy controls stemming from peripheral blood mononuclear cells (PBMCs) of which 155 were upregulated while 229 were downregulated. Subsequently, circRNA_004662 was verified to have a higher expression in CD than that in UC, which may be a novel predictive factor in distinguishing CD from UC [74]. The expressions of circRNAs in CRC have also been reported. Making use of four pairs of CRC and adjacent normal mucosa tissues, 21458 circRNAs were detected; further analysis by RNA sequencing indicated that 394 significantly upregulated and 54 significantly downregulated circRNAs existed in CRC tissues [75].

Recent articles indicate that circRNAs participate in intestinal epithelial barrier and immune homeostasis dysregulation, which is an important mechanism to facilitate the occurrence of IBD. For example, it was reported that the expression of circRNA-102685 in the colon of CD patients significantly increased, and according to the prediction of KEGG pathway, circRNA-102685 may affect apoptosis, TLR and p53 signaling pathways through sponging miRNA-146 which can affect the functions of a variety of immune cells such as Tregs and dendritic cells and trigger abnormal intestinal immune response [76]. On the other hand, the self-renewal of intestinal stem cells (ISCs) required the function of circPan3 through the IL-13Rα1-mediated signaling pathway. CircPan3 deficiency in Lgr5+ ISCs may impair ISC self-renewal and epithelial regeneration in humans [76].

CircRNAs as diagnostic and prognostic biomarkers of IBD

There are few reports on circRNAs regulatory effects in IBD. It has been considered a novel biomarker for IBD diagnosis as a result of the increased expression of certain circRNAs like circ_103516, which also showed a positive correlation with disease activity (CD activity index, Mayo, and erythrocyte sedimentation rate) and inflammatory cytokines such as TNF-α and IFN-γ, and negative correlation with anti-inflammatory cytokine IL-10 [77]. CircRNA_103516 levels in peripheral blood mononuclear cells (PBMCs) can be considered an ideal candidate biomarker for diagnosing IBD. Dysregulation of circRNA_103516 may participate in the molecular mechanism of IBD through sponging hsa-

miR-19b-1-5p which mediates inflammatory and immune-related signaling pathways. Researchers have shown that miR-19b may regulate the production of chemokines in intestinal epithelial cells by inhibiting cytokine signaling inhibitor 3, thus participating in abnormal inflammatory responses [65].

Additionally, by means of large numbers of bioinformatics analyses and experiments, Wang and colleagues recently confirmed that, reduction in circ_0007919 in UC patients encouraged the expression levels of enhancer of polycomb homolog 1 (EPC1) and vasoactive intestinal polypeptide receptor 1 (VIPR1) by sponging hsa-let-7a and miR-138 [73], leading to intestinal mucosal inflammation via the inhibition of SIRT1 gene and activation the NF-κB pathway, which have been proven crucial in the pathogenesis of IBD [78]. Hsa_circ_0007919 are associated with the pathogenesis and progression of UC, with potential diagnostic and therapeutic implications. CDKN2B-AS1 expressed in human cells, is a non-coding RNA that exists in linear and circular forms [79]. It is mainly expressed in colonic epithelial cells, and are decreased in IBD. Targeted expression of both the linear and circular transcripts of CDKN2B-AS1 improves barrier function by interacting with Claudin-2 (a critical tight junction molecule) [80]. Furthermore, circRNA_004662 might be a novel candidate for differentiating CD from UC. In a circRNA-microRNA-mRNA network, it was demonstrated that circRNA_004662 correlates with mammalian target of rapamycin (mTOR) pathway which involves the activation and proliferation of T cells, restriction of pro-inflammation, and promotion of anti-inflammatory responses in monocytes/macrophages [81].

A novel lncRNA affecting CD biology can be used as potential therapeutic target. By exploring this potential, Yin and colleagues [82] showed that hsa_circRNA_102610 upregulation in CD patients could promote the proliferation and epithelial-mesenchymal transition (EMT) of intestinal epithelial cells via sponging of miR-130a-3p, which is needed for the inhibition of transforming growth factor-β1 (TGF-β1)-induced EMT. Thus, hsa_circRNA_102610 may serve as a potential target for CD therapy and novel drug research for other related diseases. In spite of these great efforts and discoveries, the exact mechanisms linked with circRNAs effects far remain unexplored; further studies are needed.

CircRNAs as biomarkers in colorectal cancer

Compared with IBD, more circRNAs have been implicated in the development and metastasis of CRC. It has been demonstrated that circPACRGL enhanced the proliferation, migration and invasion of CRC cells, as well as the differentiation of N1 and N2 granulocytosis through miR-142-3p/miR-506-3p-TGF-β1 axis [83]. High levels of TGF-1 have been reported to promote the transformation of neutrophil phenotype from N1 to N2, while tumorigenic N2 neutrophils promote tumor proliferation and metastasis, an indication of its carcinogenic role in CRC.

CircRNA_ACAP2 [84] and circCCDC66 [85] are highly expressed in the colon tissue of CAC patients. These studies showed that circRNA-ACAP2/hsa-miR-21-5p/Tiam1 regulatory feedback loop could affect the proliferation, migration and invasion of colon cancer SW480 cells. This could be due to the fact that CircRNA-ACAP2 can regulate T-cell Lymphoma Invasion, and Metastasis-inducing Protein 1 (Tiam1) expression as miRNA sponge by removing the inhibitory effect of mir-21-5p on Tiam1 expression [84]. Hsa_circ_0000069 [86], hsa_circ_0020397 [87], and hsa_circ_001569 [88] can promote the expression of cancer cells by improving the survival rate of the cells, inhibiting apoptosis, and increasing the invasiveness of CAC cells. Loss of function assays revealed that circ_0000069 [86] could promote CRC cell proliferation, invasion, and migration. Knockdown of hsa_circ_0000069 notably induced G0/G1 phase arrest of cell cycle in CRC cells in vitro, but the exact regulation mechanism in the progress of CRC needs further investigation. Hsa_circ_0020397 [84] inhibits the activity of miR-138 by promoting the expression of miR-138 targets: telomerase reverse transcriptase (TERT) and programmed death-ligand 1 (PD-L1), thereby regulating the viability, apoptosis and invasion of CRC cells.

Xie and colleagues reported that hsa_circ_001569 functions as a sponge of miR-145, and can upregulate the expression of miR-145 functional targets transcription factor E2F5, BAG family molecular chaperone regulator 4 (BAG4) and formin-like protein 2 (FMNL2), leading to a

significant effect on CRC tumor progression. A similar study [89] also found that the expression of has_circ_0004585 in patient tissues and peripheral blood was significantly up-regulated, and the level positively correlated with tumor size, indicating the function of hsa_circ_0004585 in CRC carcinogenesis and metastasis. The study proved that circ_0004585 has the potential to be a novel diagnostic marker and therapeutic target for CRC. In their experiment, Xu and colleagues [90] demonstrated that the expression of circRNA_0001178 and circRNA_0000826 were significantly upregulated by using high-throughput sequencing and in bioinformatics analysis of clinical colon cancer patients' samples. Additionally, the study also showed that there are differentially expressed circRNAs between tissue samples of CAC patients with or without liver metastasis. CircRNA_0001178 and circRNA_0000826 can also serve as potential biomarkers for liver metastasis of CRC.

On the other hand, increased expression of certain circRNAs have been closely linked with good prognosis and tumour suppression. As documented by Li and colleagues [75], circDDX17 plays a role as tumor suppressor in CRC. In vitro experiments showed that silencing circDDX17 leads to the proliferation, migration and invasion of CRC cells, and inhibits cell apoptosis. Further bioinformatic analyses indicated that it could potentially bind to hsa-miR-21-5p, involved in both the KEGG pathways of CRC and certain microRNAs in cancers. The decreased expression of circDDX17 in CRC tissues is associated with poor or unfavorable clinical prognosis. The downregulation of expression levels of hsa_circ_103809 and hsa_circ_104700 in cancer tissue is also significantly correlated with the metastasis, differentiation, and perineural infiltration of CRC in patients [91].

CircHIPK3, a promising prognostic marker of CRC is known to promote CRC growth and metastasis by sponging miR-7 [92]. The results of this study established a strong evidence that the transcription of c-Myb enhances the expression of circHIPK3, and circHIPK3 in turn acts as an oncogenic circRNA by inhibiting miR-7. The transcription factor c-Myb is an upstream regulator of circHIPK3 expression, making the target of the c-Myb/circHIPK3/miR-7 axis a potential therapeutic strategy to combat CRC. The overexpression of circBANP in CRC is also recommended as a prognostic and therapeutic marker, but its specific mechanism of action in CRC is still unclear [93]. The promoting effect of CCDC66 on the growth and metastasis of CAC has also been documented [94]. CCDC66 which controls cell proliferation, migration, anchorage-independent growth, and other pathological processes, is upregulated in polyps and colon cancer. CircCCDC66 serves as a sponge to protect multiple oncogenes from being attacked by miRNAs, which negatively correlates with clinical treatment outcomes and poor prognosis. The study of Li and colleagues [94] showed that hsa_circRNA_102958 is highly expressed in CRC tissues. It could be linked with the promotion of the proliferation, migration, and invasion of CRC cells through the hsa_circRNA_102958/miR-585/CDC25B axis to cause carcinogenesis, and can be used as a poor prognostic marker.

Table 1 shows the progress documented in the role of different circRNA in IBD and related CRC. As more circRNAs related to IBD and its associated-CRC are being discovered, there is the provision of many potential therapeutic and prognostic biomarkers for the clinic, as well as new therapeutic targets.

Conclusion

IBD has become one of the current research hotspots in gastroenterology due to the increasing incidence, unknown etiology, and high risk of intestinal cancer transformation. CRC is a common malignant tumor ranked second in gastrointestinal cancers that seriously affects the quality of life of people. The diagnosis and treatment of IBD and its associated-CRC have been perplexing in the clinical setting. With the in-depth study of circRNA, scholars have discovered its important role in the progress of IBD and CRC. This is particularly significant since it offers a promising window of opportunity to identifying potential diagnostic and treatment options for IBD and its associated-CRC. In recent examples, studies have shown that while circRNA_0001178 and circRNA_0000826 can be used as diagnostic indicators for CRC with or without liver metastasis [91], the silencing of CircDDX17 [92] has a tumor suppressing effect on CRC, suggesting its role in the treatment of CRC. Additionally, the high stability of circRNA expression, its presence in

Table 1. Progress in the role of circRNA in IBD and its associated CRC

circRNA	Regulation trend in IBD or CRC	Mechanism and Function	Clinical significance	Reference
circ_103516	Upregulated in IBD	Dysregulation of circRNA_103516 may participate in the molecular mechanism of IBD through hsa-miR-19b-1-5p sponging, which shows a positive correlation with disease activity and inflammatory cytokines such as TNF-α and IFN-γ.	A novel biomarker of IBD diagnosis.	[77]
circ_0007919	Downregulated in UC	Enhances the expression levels of EPC1 and VIPR1 by sponging let-7a and miR-138; related to clinical characteristics and epithelial integrity.	Potential diagnostic and therapeutic implications.	[73]
circ_004662	Upregulated in IBD	Correlated with mammalian target of rapamycin (mTOR) pathway which involved in the inflammation and activation of intestinal T cells.	Preferable diagnostic biomarker of CD and novel candidate for differentiating CD from UC.	[74]
CDKN2B-AS1	Downregulated in IBD	Exhibites inhibitory effects in colonic epithelial cell proliferation by interacting with claudin-2 that can decrease barrier function.	A novel lncRNA affecting UC biology.	[80]
circ_102610	Upregulated in CD	Promote the proliferation and EMT of intestinal epithelial cells via sponging of miR-130a-3p, trigger intestinal fibrosis accompanying CD.	Serve as a potential target for CD therapy and novel drug research.	[82]
circPACRGL	Upregulated in CRC	Enhances the proliferation, migration and invasion of CRC cells, as well as the differentiation of N1 and N2 granulocytosis through miR-142-3p/miR-506-3p-TGF-β1 axis.	Promoting role in the course of CRC.	[83]
circ_0000069 circ_0020397 circ_001569	Upregulated in CRC	Promote the expression of cancer cells and improve the survival rate, apoptosis rate and invasiveness of CAC cells.	Potential diagnostic markers.	[86-88]
circ_0004585	Upregulated in CRC	Positively correlated with tumor size.	Potential diagnostic marker.	[89]
circ_0001178 circ_0000826	Upregulated in CRC	Not available.	Used as potential biomarkers for liver metastasis of CRC.	[90]
circDDX17	Downregulated in CRC	Potentially binds to miR-21-5p, and participates in the KEGG pathways of CRC.	Tumor suppressor and a therapeutic target for CRC.	[75]
circ_103809 circ_104700	Downregulated in CRC	Related to the metastasis, differentiation, and perineural infiltration of CRC.	Potential diagnostic and prognostic marker.	[91]
circBANP	Upregulated in CRC	Knockdown of circBANP with siRNA significantly attenuate the proliferation of CRC cells.	Serve as a prognostic and therapeutic marker.	[93]
CCDC66	Upregulated in CRC	Controls cell proliferation, migration and anchorage-independent growth.	Negatively correlated with poor prognosis.	[85]
circ_102958	Upregulated in CRC	Promote the proliferation, migration and invasion of CRC cells through circRNA_102958/miR-585/CDC25B axis.	Potential prognostic marker.	[94]

body fluids, and specific role in diseases make it a promising biomarker in disease diagnosis, treatment, and prognosis including IBD. With the current limited research on the latest progress of circRNAs in IBD and its related CRC, there is the need for more focus driven and large study exploration in this field.

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Disclosure of conflict of interest

None.

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