Emerging role of small RNAs in inflammatory bowel disease and associated colorectal cancer (Review)

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Abstract. Inflammatory bowel diseases (IBDs), which encompasses Crohn's disease and ulcerative colitis, is a chronic inflammatory condition associated with an increased risk of colorectal cancer (CRC). Small RNAs have been linked to various illnesses, including IBD and CRC. These small RNAs also serve as potential biomarkers for these diseases, offering a cutting-edge approach to investigating possible treatments. To date, treatments involving oral nucleic acid usage are still unachievable due to the instability of medications in the gastrointestinal tract (GIT), their lack of ability to effectively target disease tissues and their notable adverse effects. However, nanoparticle or exosome delivery systems of nucleic acid medications effectively target disease tissues by overcoming the instability of the GIT, resulting in an effective outcome. In the present review, the biogenesis of small RNAs (tRNA-derived small RNA, microRNA, small nucleolar RNA and p-element-induced wimpy testis-interacting RNA), their roles in the pathogenesis of IBD and CRC as well as their application as possible diagnostic and prognostic biomarkers in IBD and CRC are discussed.

Contents

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1. Introduction

Inflammatory bowel diseases (IBDs), which include Crohn's disease and ulcerative colitis (UC), are chronic inflammatory illnesses of the gut (1) that are associated with high levels of intestinal epithelial cell (IEC) mortality, which weakens the gut barrier, activates immune cells and causes further IEC death (2). IBD is believed to be significantly influenced by the immune system, gut microbiota and genetic makeup of patients (3). Depending on the disease location, type and intensity, symptoms can include bleeding, diarrhea, abdominal pain, fever and weight loss (4). The burden of IBD is expected to increase due to aging and population expansion until 2050, which highlights the need to address the changing public health concern that IBD poses (5). Despite recent declines in the prevalence of colorectal cancer (CRC), patients with IBDs are more likely to develop CRC (6). Globally, CRC accounts for the second highest incidence of cancer cases and ranks third in terms of cancer-related death (7). In 2020, 1,931,590 new cases of CRC were reported, with 935,173 deaths (8). The evolution of neoplastic lesions is fueled by chronic inflammation, which can lead to dysplastic precursor lesions that may develop in different colonic locations as a result of field cancerization (6).

RNA regulators, such as riboswitches and small RNAs, regulate gene expression in response to environmental or metabolic changes (9). Small RNA species include tRNA-derived small RNA (tsRNA), small interfering RNA (siRNA), microRNA (miRNA/miR), small nucleolar RNA (snoRNA) and p-element-induced wimpy testis (PIWI)-interacting RNA (piRNA/piR) (10,11). miRNAs, which are small non-coding

RNAs (sncRNAs), influence a number of molecular pathways implicated in the pathobiology of IBD (12), and accumulated data suggests that they are essential to the development and spread of CRC (13). Additionally, new evidence suggests that snoRNAs are notable regulatory molecules implicated in several pathophysiological events, such as cancer and inflammation (14). Therefore, evaluating the level and function of snoRNA expression has potential applications in CRC diagnosis and prognosis (15), as well as IBD. The expression of piRNAs, a unique class of sncRNAs, has been demonstrated to be dysregulated in several malignancies; however, it is yet unclear what their clinical significance is in CRC (16). Additionally, new non-coding short RNAs termed tsRNA are abundant and persistent in bodily fluids, and they may have a variety of biological regulatory functions (17). Thus, the emergence of small RNAs in the pathogenesis of IBD and CRC and their use as biomarkers may offer therapeutic strategies for these diseases. Notably, antisense oligonucleotides and siRNAs have also demonstrated significant promise in treating human diseases (18), including IBD and CRC.

Regardless, oral administration of nucleic acid for treatments is still unreachable (19), and this approach has faced numerous obstacles, such as the instability of the medication in the gastrointestinal tract (GIT), their inadequate ability to target disease tissues and their notable adverse consequences (20). Nonetheless, colitis tissue-targeted distribution and location-specific medication release enabled by nanoparticles may offer a new, therapeutically successful approach to meet these challenges (20). Therefore, in the present review, the roles of small RNAs (tsRNA, snoRNA, miRNA and piRNA) in the pathogenesis of IBD and CRC and their application as possible biomarkers for the prognosis and diagnosis of IBD and CRC are discussed. The present review also covers emerging therapeutic strategies for delivering nucleic acids as medications in IBD and CRC by overcoming GIT instability.

2. From IBD pathogenesis to cancer

IBD can progress to cancer due to factors such as mucosal inflammatory mediators, genetic and epigenetic influences, oxidative stress, intestinal microbiota and oncogenic signaling pathway activation. These factors have been explained further below. Fig. 1 illustrates the potential progression of IBD to cancer and other aspects.

Mucosal inflammatory mediators. Chronic inflammation is a hallmark of IBD, which damages the DNA of epithelial cells from the colon and rectum by producing more free radicals and inflammatory cytokines such as tumor necrosis factor-α (TNF-α) (21). Cytokines, produced through persistent inflammatory responses and signaling pathways, enable cancer-prone cells to avoid apoptosis and progress from dysplasia to CRC (21). In addition, inflammation can induce mutagenesis, and its recurring pattern, paired with epithelial renewal, may exert selection pressure that hastens cancer growth (22).

TNF-α. The pro-inflammatory mediator, TNF-α, regulates cell-to-cell communication in the tumor microenvironment and can potentially induce the metastatic phenotype (23). A meta-analysis study indicates that the TNF-α 308G>A gene polymorphism significantly influences the susceptibility of patients to Crohn's disease and UC (24). Another study found that TNF-α messenger RNA (mRNA) expression is higher in CRC than in normal colorectal tissues. The study also revealed that TNF-α gene expression is higher in stage III and IV neoplasms compared with earlier tumor stages (25). These findings imply that TNF-α may contribute to IBD pathogenesis and its progression to CRC. A recent study revealed that TNF may stimulate the formation of neoplastic lesions at the start of colitis-associated colon cancer (CAC) and decrease them as the disease progresses. *TNF* deletion in Winnie-*Apc*$^{Min/+}$ mice reduced dysplastic lesions in 5-week-old mice, followed by a faster disease progression at 8 weeks (26). This supports the theory that TNF may be implicated in the progression of IBD to CRC.

Cyclooxygenase-2 (COX-2). Nuclear factor-κB (NF-κB) may contribute to the progression of CRC by regulating the expression of target genes involved in angiogenesis, including COX-2 (27). COX-2, a key player in tumor progression, has been identified as a potential therapeutic target for numerous human and animal cancer types (28). A study found that COX-2 is upregulated along the neoplastic spectrum in UC (29). This may imply that COX-2 is involved in the IBD transition to CRC. In a different study, Gregório *et al* (28) discovered that COX-2 serves a role in the angiogenesis and inflammatory environment establishment that promotes the growth of melanoma tumors. Another study found that hydroxyeicosatetraenoic acids may increase colonic inflammation and CRC risk in IBD by directly and indirectly inducing COX-2-mediated prostaglandin production (30). A recent study found that *Clostridium butyricum* inhibited CAC in mice as well as reduced COX-2 levels and phosphorylated NF-κB (31). These data suggest that COX-2 may be implicated in IBD progression to malignancy.

IL-6. The pro-inflammatory cytokine, IL-6, interacts with soluble or membrane-bound IL-6 receptors (IL-6Rs) to communicate via glycoprotein 130 (gp130) in *trans* or *cis* directions (32). IL-6 is a versatile cytokine with wide-ranging effects on the integrated immune response, hematopoiesis and oncogenesis (33,34). Wu *et al* (35) discovered that miRNA-320 targets IL-6R and reduces carcinogenesis in mice with CAC by decreasing IL-6R expression. Another study also found that patients with active UC, dysplasia and malignancy exhibit significantly higher IL-6 and phosphorylated-signal transducer and activator of transcription 3 (p-STAT3)-positive epithelial cells than the controls (36). These results further affirm the role of inflammatory mediators in IBD progression to cancer.

IL-23. IL-23, a pro-inflammatory cytokine, has been linked to various health issues, including plaque psoriasis, chronic obstructive pulmonary disease, UC and CRC, and regulates T helper (Th)-17 inflammation (37-40). According to Ljujic *et al* (41), serum IL-23 levels are markedly higher in patients with CRC than in healthy individuals. These levels are strongly linked to vascular endothelial growth factor (VEGF) upregulation, which suggests that IL-23 may play a role in the development of CRC. Another study by Wu *et al* (42) found that synbiotic medication can safeguard the intestinal barrier and prevent the occurrence of CAC. The synbiotic could notably block aberrant activation of the intestinal wingless-related integration site (Wnt)/β-catenin signaling pathway, which is highly connected to IL-23 (42).

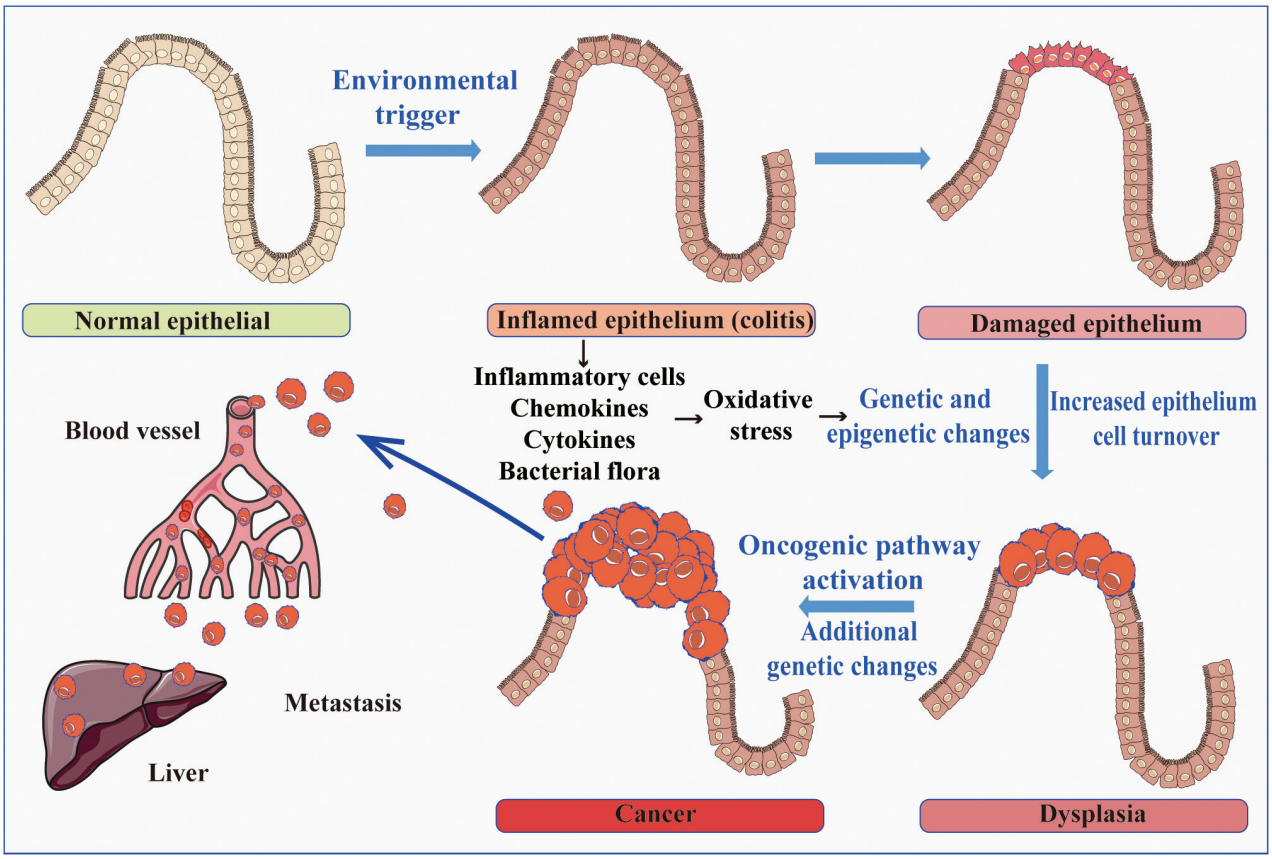

Figure 1. Mechanism of inflammatory bowel disease pathogenesis to colorectal cancer. Environmental factors such as infections, toxins and diet may cause the normal epithelium to become inflamed (colitis). Colitic epithelium triggers the production of inflammatory cells, cytokines and chemokines and alters the gut flora, leading to increased oxidative stress. Oxidative stress causes damage to the inflamed colon and triggers genetic and epigenetic changes that transform the damaged epithelium into abnormal epithelium (dysplasia). Additional genetic changes transform the abnormal cells into cancer, causing colitis-associated cancer. Abnormal cells can spread (metastasis) to other organs such as the liver.

Chemokines. Chemokines, also known as chemotactic cytokines, are small released proteins that signal via G protein-coupled heptahelical receptors on the cell surface (43). These molecules play a crucial role in the inflammation-related pathophysiology of rheumatoid arthritis, cancer, insulin-resistant diabetes, atherosclerosis, neurological disorders and IBD (44). Mrowicki *et al* (45) found that IBD may develop more frequently in those with polymorphisms in the C-X-C motif chemokine receptor *(CXC)R4*/C-X-C motif chemokine ligand *(CXCL)12* chemokine axis. Patients with IBD experience inflammation due to the interaction between the G-protein-coupled receptor, CXCR4, and CXCL12, a G-protein natural ligand (46). CXCR4 triggers various processes, including clonogenic growth stimulation, VEGF release induction and intercellular adhesion molecule-1 upregulation in CRC (47). According to data from Ottaiano *et al* (47), suppressing CXCR4 prevents CRC metastasis. This implies that CXCR4 may be associated with IBD pathogenesis and its progression to CRC metastasis. A systematic study found that patients with CRC who have upregulated CXCR4 expression have a significantly lower overall and disease-free survival (48). Additionally, Cheng *et al* (49) found that CXCL3 is increased in colon adenocarcinoma (COAD) tissues. CXCL3 is essential for controlling the malignant tendencies of tumor cells (49). Therefore, CXCL3 is involved in the pathogenesis of COAD.

Immune cells. Immune cells play a crucial role in both the acute and chronic stages of IBD, as they facilitate the progression of the disease from inflammation to carcinogenesis (50). Immune cells such as macrophages, T cells, regulatory T cells (Tregs), natural killer T (NKT) cells, innate lymphoid cells (ILCs), neutrophils and other T cell subsets play a role in this transitioning process. For instance, obesity-induced IL-6 shifts macrophages toward those that promote tumors and release the chemokine, C-C motif chemokine ligand 20 (CCL20), in the CAC microenvironment (51). As a result, CCL20 facilitates the advancement of CAC by attracting B cells and γδ T cells that express CCR6 by chemotaxis (51). Additionally, IL-6 secretes granulocytic-myeloid-derived suppressor cell (MDSC) exosomal miR-93-5p, promoting monocytic-MDSC differentiation into M2 macrophages via STAT3 signaling, facilitating the transition from colitis to cancer (52). These results demonstrate how macrophages function in CAC.

Moreover, Zhang *et al* (53) found that patients with UC and high neutrophil infiltration subtype B levels are more likely to acquire CAC. Therefore, neutrophils have been suggested to facilitate the conversion of UC into CAC. Burrello *et al* (54) found that patients with IBD have invariant NKT (iNKT) cells in their lamina proprias, exposed to mucosa-associated bacteria, causing pro-inflammatory activation and pathogenic actions against the epithelial barrier. Díaz-Basabe *et al* (55) also revealed that *Porphyromonas gingivalis* (pathobiont)

triggers iNKT cells to upregulate chitinase 3-like-1 protein, limiting cytotoxic functions, promoting immune evasion and accelerating the progression of CRC. These results show that iNKT cells may be involved in the pathogenesis of CRC and IBD.

According to another study, the generation of colorectal IL-22 requires butyrophilin-like protein 2 (BTNL2). BTNL2 stimulates the production of IL-22 via acting on ILC3s, $CD4^+$ T cells and γδ T cells. BTNL2 knockout mice have lower colonic carcinogenesis and more severe colitis phenotypes than control mice due to IL-22 production defects (56). This may imply that ILC3s, $CD4^+$ T cells and γδ T cells are involved in CAC. Additionally, CD14 has also been found to enhance colon cancer stem cell proliferation, metastasis and carcinogenesis in response to lipopolysaccharide (LPS) stimulation via the toll-like receptor 4 (TLR4)/myeloid differentiation factor 88 (MyD88) signaling pathway (57). Other studies indicate that $ROR\gamma t^+$ Treg (58) and Vδ2 T cells (59) are implicated in IBD, CRC and CAC.

Oxidative stress. In total, 25% of human malignancies are caused by persistent oxidative damage during inflammation (60). During inflammation, inflammatory and epithelial cells produce reactive nitrogen species and reactive oxygen species (ROS) that can harm DNA (60). Studies suggest that oxidative stress and DNA damage may increase the likelihood of IBD advancing to cancer (61,62). In malignancies, nitric oxide (NO) has pro- and antitumor properties. Endogenous NO levels can promote colon cancer, while prolonged exogenous doses can have lethal effects (63). NO is crucial in various CRC signaling pathways, such as extracellular signal-regulated kinase and Wnt/β-catenin, which are linked to the development, spread and resistance to chemotherapy and radiation of CRC (63). One of the three essential enzymes that produce NO from the amino acid, L-arginine, is inducible NO synthase (iNOS) (64). When *Helicobacter hepaticus* (Hh) infects recombination activating gene 2-deficient ($RAG2^{-/-}$) mice, colitis develops and eventually turns into lower colon cancer. NO, a chemical with documented mutagenesis potential, is crucial in this mechanism (65). Wang *et al* (65) further found that $RAG2^{-/-}$ mice infected with Hh rapidly produce iNOS and develop DNA double-strand breaks, a unique characteristic of growing crypt epithelial cells. A similar study by Erdman *et al* (66) found that when Hh infects $RAG2^{-/-}$ mice, the colon is infiltrated with macrophages and neutrophils. These activities are correlated with the upregulation of iNOS expression and NO generation, as shown by the urine excretion of nitrite. The modifications result in a progressive rise in severe inflammation, hyperplasia, dysplasia and malignancy. Therefore, iNOS and NO may cause IBD to transition to cancer.

Genetic mutations. *TP53*, commonly termed the 'guardian of the genome', is an important tumor suppressor gene (67). The *TP53*-encoded p53 protein acts as a sensor of DNA damage in cells, alerting them when necessary (67). It has long been hypothesized that the primary mechanism by which mutant p53 contributes to carcinogenesis is its decreased capacity to trigger apoptosis, DNA repair and cell cycle arrest in response to carcinogenic stimuli (68). *TP53* mutations are prevalent in various malignancies, including lung, breast and colon cancer (67). A systematic review found that patients with IBD-CRC have a higher frequency of *TP53* mutations than those with sporadic (S)-CRC (69). In IBD-CRC, *TP53* mutations tends to be more significant than *KRAS* (in terms of frequency and disease pathology), in contrast to S-CRC (69).

Loss of heterozygosity, somatic mutation, decreased expression and enhanced alternative splicing into a dominant negative oncogenic splice variant, Kruppel-like factor 6 (KLF6)-SV1, inactivates the *KLF6* tumor suppressor gene in a number of human malignancies (70). A study found that most sporadic and IBD-related CRC cases have inactivated KLF6 due to loss or mutation. At least 55% of tumors have a deleted *KLF6* locus and 44% have alterations, with loss and mutation rates comparable to *TP53* and *KRAS* (71). Additionally, gastric cancer has been linked to *KLF6* locus-specific deletion (70). Therefore, *TP53*, *KRAS* and *KLF6* loss or mutation may lead to IBD-CRC.

Epigenetic changes. Epigenetics, including DNA methylation, has been linked to the progression of IBD to cancer. DNA methylation is a crucial epigenetic method that allows cells to regulate gene transcription (72). Certain genes undergo either hypermethylation (increased methylation) or hypomethylation (decreased methylation) in response to DNA methylation. Increased methylation decreases gene expression, while decreased methylation increases gene expression, affecting the function of the genes. In cases of tumor suppressor genes, hypermethylation silences their tumor suppressor action while hypomethylation increases their tumor suppressive roles.

The gene, adenomatous polyposis coli (*APC*), is a tumor suppressor that regulates the Wnt signaling pathway, and inhibition of *APC* promotes CRC (73,74). According to Dhir *et al* (75), Wnt signaling pathway gene methylation is a common early event in IBD and IBD-related neoplasia. It was further found that IBD-associated neoplasia has markedly greater levels of methylation of *APC1A*, *APC2*, secreted frizzled-related protein (*SFRP)1* and *SFRP2* than IBD colitis. Therefore, the transition from IBD colitis to IBD-associated neoplasia is characterized by *APC1A, APC2, SFRP1* and *SFRP2* methylation (75). Several genes, including Forkhead box protein *(FOX)E1* and spectrin repeat-containing nuclear envelope protein 1 (76), fragile histidine triad (77) as well as transcription elongation regulator 1-like gene (78,79), have been linked to the progression of IBD to colon cancer due to methylation changes.

Intestinal microbiota. The dynamic and varied microbial community of the human GIT is essential to health, with the gut microbiota fostering the growth and operation of the gut immunological barrier (80). CAC, a type of CRC, is tightly linked to gut microbiota dysbiosis and chronic inflammation (81). Uronis *et al* (82) showed that CAC development depends on the gut microbiota, and chronic colitis increases the capacity of colorectal tumors to proliferate into advanced stages. Microbial identification by the TLR/MyD88 system is a prerequisite for these activities. In colitis, elevated TLR4 signaling stimulates dual oxidase 2 expression and hydrogen peroxide generation by epithelial cells. The local environment influences the mucosal microbiota, leading to pathogenic

characteristics such as elevated ROS levels in the epithelium and a rise in colitis-associated tumors (83). In summary, CAC is caused by ROS in the epithelium, triggered by innate immunological signaling in response to the mucosal microbiota (83). For colon cancer development in chronic colitis, TLR4 signaling is essential (84). Therefore, the interaction of the gut microbiota with TLR signaling may be crucial for therapeutic purposes in treating CAC.

Signaling pathways

NF-κB. IBDs, including UC and Crohn's disease, are associated with the CRC subtype, CAC. The NF-κB-triggered signaling pathway is a significant factor associated with colonic inflammation (85). Additionally, one important regulator of CRC cell proliferation, apoptosis, angiogenesis, inflammation, metastasis and treatment resistance is the NF-κB signaling system. CRC involves over-activation of the NF-κB pathway (86). Lu *et al* (87) revealed that RING finger 138 (RNF138)$^{-/-}$ mice are more susceptible to aggressive cancer transition due to persistently abnormal NF-κB signaling in colonic cells, indicating a potential risk factor for colitis. The study demonstrated that inhibiting NF-κB signaling effectively prevented tumor formation of CRC cells deficient in RNF138 or from patients with dysregulated RNF138 (87). Additionally, NF-κB pathways have been shown to be involved in CAC and CRC (88-90). This implies that NF-κB signaling may be involved in the colitis transition to CRC.

Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR). PI3K/AKT/mTOR is a key pathway in cancer that regulates cell size, growth, proliferation, motility and metabolism (91,92). Studies have demonstrated that the PI3K/AKT/mTOR pathway is implicated in the development of CAC. For instance, a recent study found that in CAC model mice, the expression levels of p-PI3K, p-AKT and mTOR are significantly elevated. However, the group treated with Huangqin Tang (HQT), a Chinese medicinal compound, had lower levels of p-PI3K and p-AKT than the model group. HQT significantly inhibited the PI3K/AKT/mTOR pathway, potentially enhancing apoptosis and inhibiting cell growth (93). Another study also discovered that the CAC mouse model has considerably higher p-PI3K/AKT levels. However, Wumei Wan, a Traditional Chinese Medicine, effectively prevented cancer by blocking the stimulation of PI3K and AKT (94). These results imply that the PI3K/AKT/mTOR pathway may be involved in the development of colitis into cancer.

STAT3. The primary mediator of cytokine signaling of the IL-6 type, STAT3, is a crucial transcriptional regulator of cell division, maturation and survival (95). Liu *et al* (96) found that tea polysaccharides (TPS) inhibit the progression of CAC by inhibiting the IL-6/STAT3 axis and the expression of downstream genes. TPS significantly reduced tumor incidence and size and inhibited pro-inflammatory cell infiltration and cytokine release by balancing the cellular microenvironment. Similarly, Saadatdoust *et al* (97) found that a dietary cocoa partially mediates the suppression of CAC carcinogenesis by limiting IL-6/STAT3 activation. These results suggest a critical role for the IL-6/STAT3 axis in modulating the relationship between colitis and cancer.

3. Biogenesis of small RNAs

Primary piRNA. RNA polymerase II pre-initiation complex development within repressive heterochromatin in drosophila enforces the transcription of piRNA clusters, tiny RNA source loci, in animal gonads (98). Primary piRNAs are found in distinct genomic regions known as piRNA clusters, and they appear to have originated from lengthy, single-stranded precursors (99). Zucchini is essential in defining the 5' and 3' ends of piRNAs in this evolutionarily conserved piRNA biogenesis process (100). Pre-piRNAs are released by aubergine or argonaute (Ago)3-mediated cleavages, which require time-consuming removal by the Nibbler exoribonuclease in the 3'-to-5' direction, while cleavages caused by Zucchini accurately determine the exact locations of mature piRNA 3' ends (101). The action of the MOV10L1 RNA helicase facilitates the unwinding and redirection of the single-stranded piRNA precursor transcripts towards the endonuclease responsible for the initial cleavage step in piRNA processing (102). The 5' end of silkworm PIWI (SIWI)-bound piRNAs is strongly biased toward uridine, and adenine is abundant at position 10 in piRNAs linked to Ago3 (BmAgo3) (103). In contrast to BmAgo3, which binds sense piRNAs, SIWI preferentially binds antisense piRNAs (103). Perinuclear Yb bodies, the sites of piRNA synthesis, are where piRNA maturation and connection with PIWI occur (104). Trimmer and Hua-Enhancer 1 (Hen1) mature pre-piRNAs regardless of the endonucleolytic process (105). Trimmer binds to Papi/Tdrkh and is abundant in the mitochondrial fraction (106). Hen1 is the enzyme that introduces the 2'-*O*-methyl modification to the 3' ends of piRNAs (107). Trimmer and Papi/Tdrkh depletion additively inhibit trimming, leading to the buildup of 35-40 nucleotide (nt) pre-piRNAs that are unstable and prone to destruction (106) (Fig. 2).

snoRNAs and small nucleolar ribonucleoproteins. Most snoRNAs in vertebrates are encoded in the introns of genes that code for proteins and are released through the exonucleolytic cleavage of linearized intron lariats (108). The spliceosome or an RNase III-like activity releases intron-encoded and polycistronic snoRNAs from primary transcripts as pre-snoRNAs (109). Via exonucleolytic activities, pre-snoRNA leader and trailer sequences are eliminated (109). A debranching activity in the spliceosomal pathway then linearizes the resultant intron lariat (109). The nucleolus, which concentrates rRNA modification guide RNAs known as snoRNAs, is where posttranscriptional modifications of rRNA occur. However, small Cajal body-specific RNAs, which guide modifications for spliceosomal small nuclear RNAs (snRNAs), accumulate in the Cajal body (110). Posttranscriptional modification of rRNAs, specifically 2′-*O*-methylation (Nm) and pseudouridylation, is the canonical function of box C/D snoRNA (SNORD) and box H/ACA snoRNA (SNORA), respectively (111) (Fig. 3).

miRNA. miRNAs, derived from sequences of DNA, are transcribed into primary miRNAs and transformed into precursors and mature miRNAs (112). Drosha, a nuclease belonging to the RNase III family, catalyzes the initial cleavage of primary miRNA transcripts (pri-miRNAs) found in the nucleus (113). RNase III domains A and B of Drosha form an intramolecular

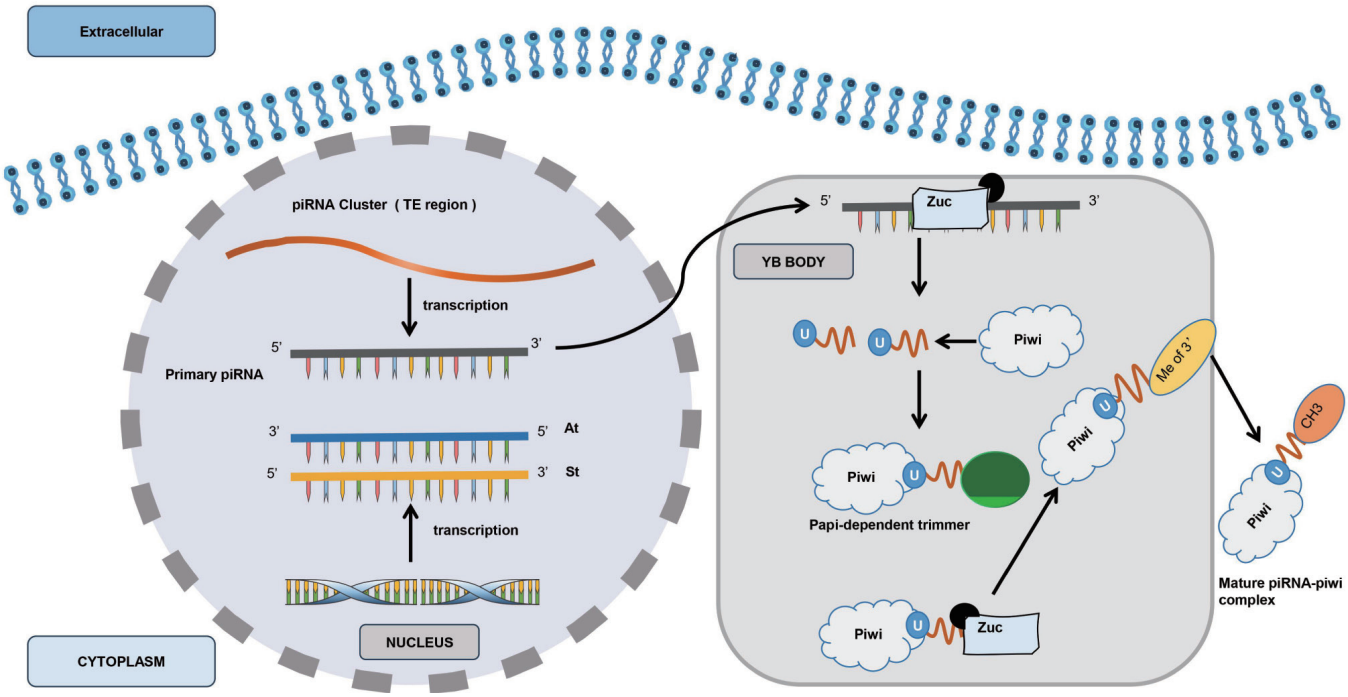

Figure 2. Primary piRNA biosynthesis. piRNA is synthesized from the piRNA transcript, reaches maturity in Yb bodies and is then methylated by the Hua-Enhancer 1 enzyme. At, antisense transcription; piRNA, PIWI-interacting RNA; PIWI, p-element-induced wimpy testis; Me, methylation; St, sense transcription; TE, transposable element; U, uridine; Zuc, Zucchini.

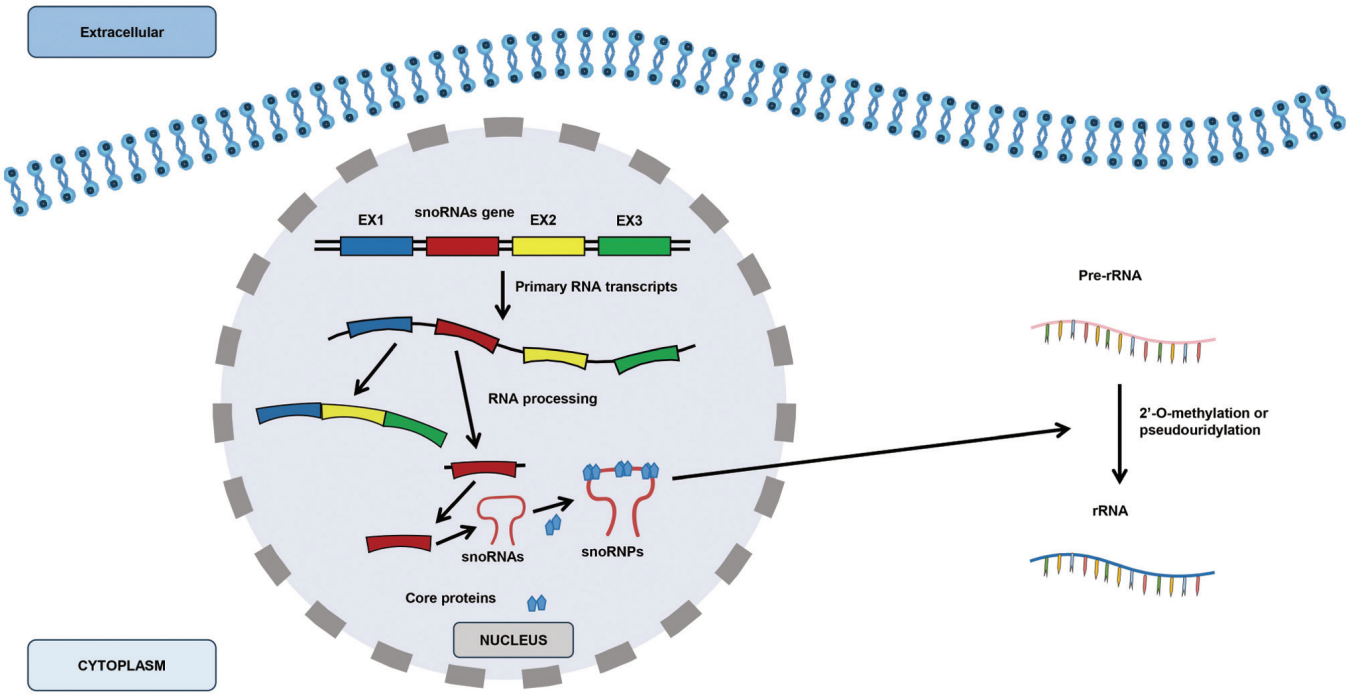

Figure 3. Mechanism for generating snoRNAs and snoRNPs. Primary RNA transcripts are converted into pre-snoRNA and then processed via a sequence of actions to form snoRNAs. Core proteins bind to snoRNAs to create snoRNPs. rRNA, ribosomal RNA; snoRNPs, small nucleolar ribonucleoproteins; EX, exon.

dimer and cleave the 3' and 5' strands of the stem, respectively. This mechanism is identical to that of human dicer (114). Post-transcriptional processing transforms each miRNA into a duplex of two strands (115). During miRNA strand selection, one of two strands is loaded into an Ago protein to create the miRNA-induced silence complex (miRISC), and the other strand of the complex collapses after being removed (115). Human RNA-induced silencing complexes, including the Ago subfamily proteins Ago1-4, are where siRNAs and miRNAs are integrated (116). miRNA must form a miRISC with an Ago protein for active function, which binds to specific mRNA through complementarity sequences (117). miRNAs

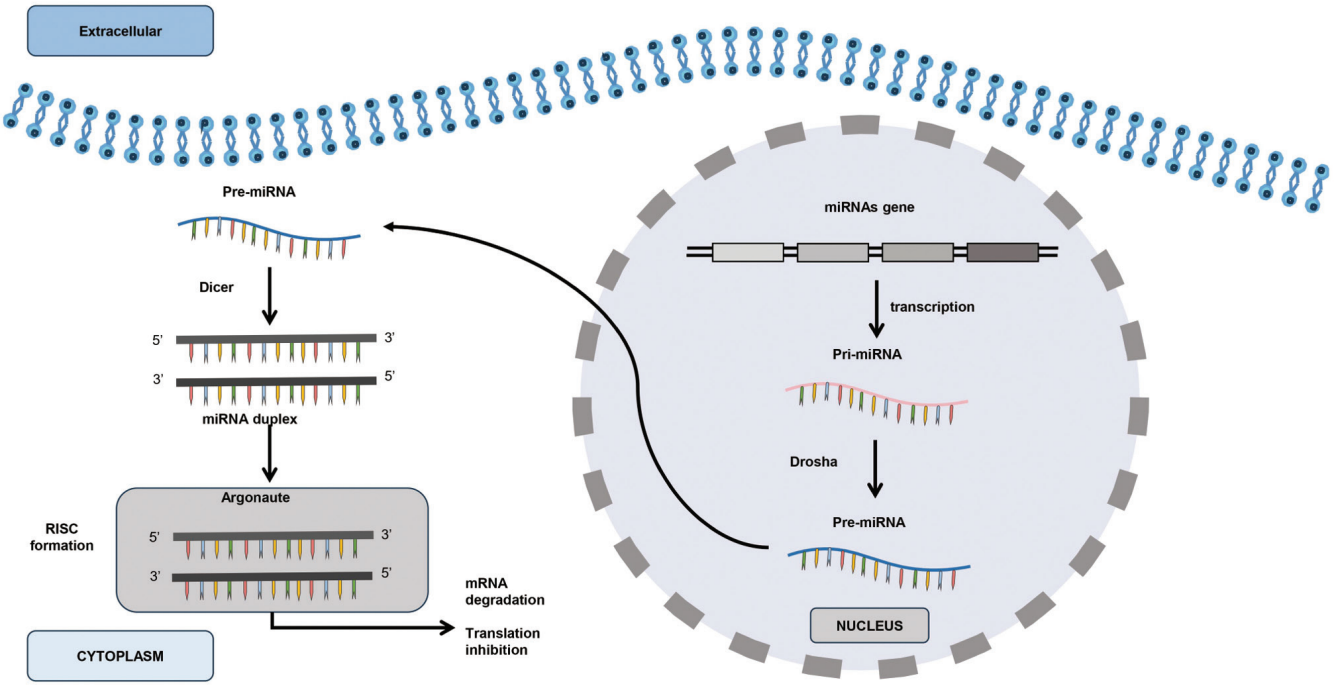

Figure 4. Biogenesis of miRNA. Drosha cleaves Pri-miRNA generated from DNA sequences to produce Pre-miRNA. Dicer then cleaves pre-miRNA to create a miRNA duplex. One strand from the duplex binds with Argonaute proteins to form miRISC. The miRISC then binds to mRNA via complementary sequences for degradation of mRNA and translation inhibition. RISC, RNA-induced silencing complex; miRNA, microRNA; Pri, primary.

often cause translational repression and mRNA degradation by interacting with the 3' untranslated region (UTR) of target mRNAs but also engage with the 5' UTR, coding sequence and gene promoters (112) (Fig. 4).

tsRNA. tsRNAs are produced from mature tRNA and tRNA precursors when tRNAs are cleaved explicitly by angiogenin (ANG) and dicer in specific tissues or cells or under certain circumstances such as hypoxia and stress (118). tRNA halves (tiRNA) and fragments produced from tRNA (tRFs) are the two subtypes of tsRNAs (119). tRFs-1, 2, 3, 5 and i-tRF, which consist of 3' and 5' tiRNA, are the five types of tRFs based on the incision loci (119). 5'-tRNA and 3'-tRNA halves are the two different forms of tRNA halves (120). The 31-40 nt-long tRNA halves are created when mature tRNAs undergo specific cleavage in their anticodon loops (120).

4. Small RNA modifications

According to available data, small RNAs can also undergo several modifications to their nucleotide composition that impact their stability and nuclear export ability. These modifications are important since they influence the ability of small RNAs to drive molecular signaling processes important for biogenesis, cell proliferation and differentiation (10) (Fig. 5). These small RNA modifications include N6-methyladenosine (m6A), Nm, 3-methylcytidine (m3C), 5-methylcytosine (m5C), N7-methylguanosine (m7G), N1-methyladenosine (m1A), and pseudouridine (Ψ).

m6A. Within eukaryotic cells, m6A is the most common co-transcriptional modification in RNAs. The m6A methyltransferases, or 'writers', such as methyltransferase-like (METTL)3/14/16, RNA-binding motif protein 15 (RBM15)/15B, zinc finger CCCH domain-containing protein 13, VIRMA, CBLL1, Wilms' tumor 1-associating protein (WTAP) and KIAA1429, modify the m6A modification. The demethylases, or 'erasers', such as fat mass and obesity-associated protein (FTO) and alkylation protein AlkB homolog 5 (ALKBH5), remove it. The proteins known as 'readers' that bind to m6A include YTH domain family (YTHDF)1/2/3, YTH domain containing 1 (YTHDC1)/2, insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1)/2/3, and heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1) (121).

METTL3 methylates pri-miRNAs to designate them for DGCR8 recognition and processing (122). HNRNPA2/B1 detects m6A pri-miRNA alteration by METTL3 or METTL14, promoting the DGCR8-pri-miRNA interaction and accelerating miRNA production (10). To perform cellular m6A deposition on mammalian nuclear RNAs, METTL3 and METTL14 form a heterodimeric complex (123,124). METTL3/14 is situated in the nucleus and is localized to nuclear speckles. The splicing regulator, WTAP, is required for this specific nuclear localization pattern (124). A study found that suppressing RBM15 and RBM15B or METTL3 is a significant barrier to XIST-mediated gene silencing (125). METTL16 has been identified as the cause of m6A deposition in certain transcripts (126). ZC3H13 (127), KIAA1429 (128), Hakai (129) and ZCCHC4 (130) are other methyltransferases that cause m6A alterations.

Two m6A demethylases, FTO and ALKBH5, have been identified, which play a crucial role in various aspects of mRNA biology, including processing, export, metabolism and stability (131). The catalytic domain of ALKBH5 has been demonstrated to demethylate single-stranded DNA and single-stranded RNA through catalytic experiments (132),

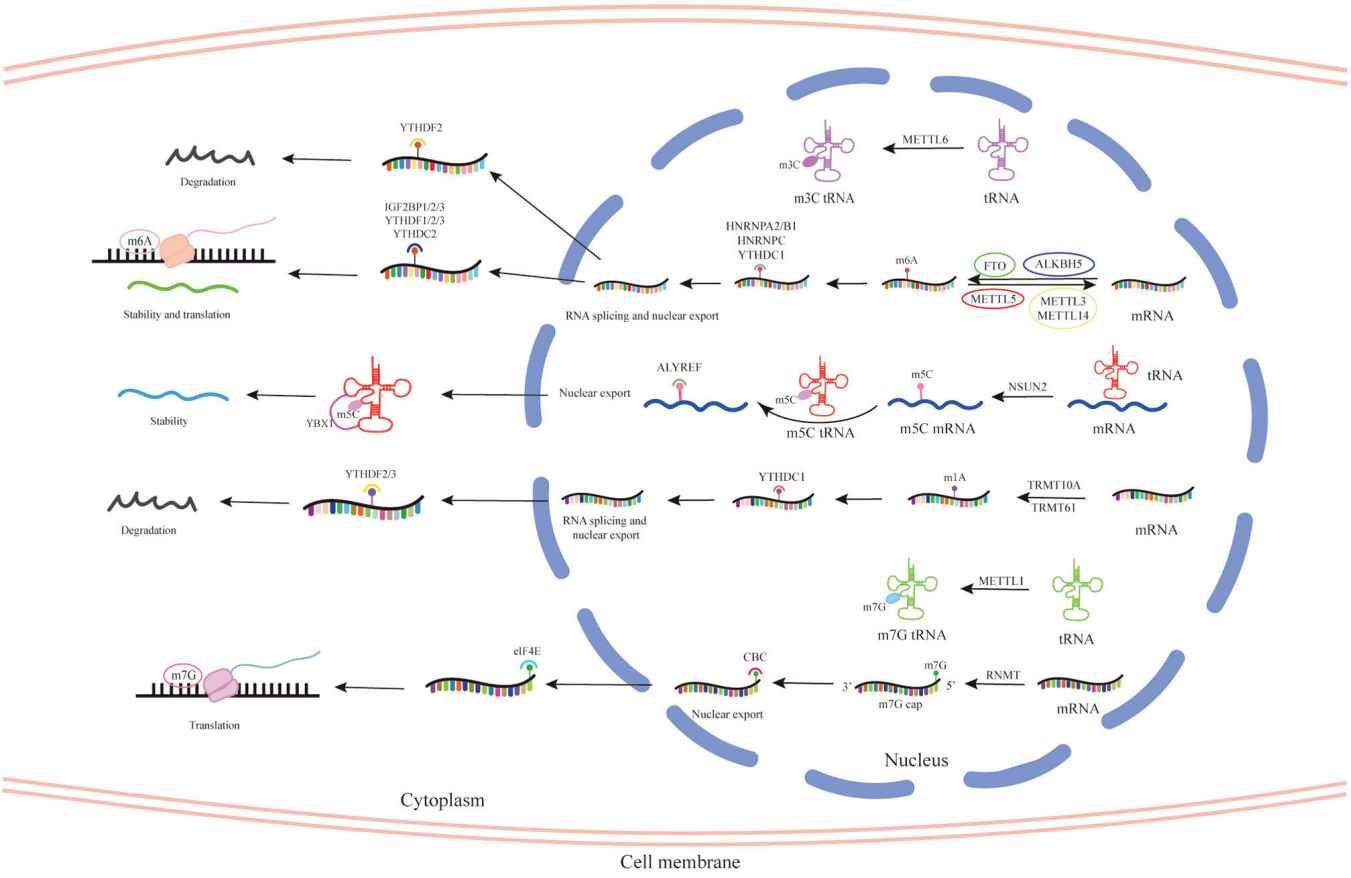

Figure 5. RNA modifications in small RNAs. Writers, readers and erasers carry out these alterations. The writers (such as TRMT10A and TRM61), readers (such as YTHDF/2/3) and erasers (such as ALKBH1/3/7) are involved in m1A. The writer, NSUN, and reader, ALYREF, are also seen in m5C. Additionally, certain writers (such as METTL3/5/14), readers (such as YTHDF1/2/3, YTHDC1/2, IGF2BP1/2/3 and HNRNPA2B1) and erasers (such as ALKBH5 and FTO) are also observed in m6A. M7G writers consist of METTTL1 and RNMT. METTL6 is the writer for m3C. ALKBH5, AlkB homolog 5; ALYREF, Aly/REF export factor; CBC, cap-binding protein complex; eIF3, eukaryotic initiation factor 3; FTO, fat mass and obesity-associated protein; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; m3C, 3-methylcytidine; m5C, 5-methylcytosine; m7G, N7-methylguanosine; METTL, methyltransferase-like; mRNA, messenger RNA; NSUN, NOP2/Sun domain; TRMT, tRNA methyltransferase; RNMT, RNA guanine-7 methyltransferase; YTHDC, YTH domain containing; YTHDF, YTH domain family.

while FTO catalyzes Fe(II) and 2-oxoglutarate-dependent modifications of nucleic acids, notably the demethylation of m6A in mRNA (133). YTHDC1, a crucial m6A nuclear reader, is vital for managing mRNA splicing, export and stability (134). HNRNPA2B1, similar to m6A writer METTL3, directly binds a set of nuclear transcripts, causing alternative splicing effects (135).

The effects of m6A are considered to be mediated through a complex network of interactions between various m6A sites and three diverse cytoplasmic YTHDF m6A-binding proteins, DF1, DF2 and DF3 (136). Other cytoplasmic readers include IGF2BP1, IGF2BP2, IGF2BP3 and eukaryotic initiation factor 3 (eIF3). IGF2BP1, IGF2BP2 and IGF2BP3 are RNA-binding proteins that contribute to development and disease by regulating the stability of mRNA and the translation of essential modulators of cell division and metabolism (137). Additionally, over the past 3 years, research has significantly enhanced the comprehension of the role of eIF3 in mRNA translation (130). A study has shown that the m6A alteration of D-3-phosphoglycerate dehydrogenase mRNA, mediated by METTL3, improves its interaction with eIF3i, thereby accelerating its translational rate (138), implying that eIF3 may be involved in mRNA translation.

Nm. Nm is a well-known RNA modification found in non-coding RNAs that has been detected at various internal locations of mRNA. Extensive Nm at internal locations of mRNA enhances mRNA stability (139). RNA Nm, a common feature in non-coding RNAs such as rRNA, tRNA and snRNA, is found at the 5' cap of most mRNAs in higher eukaryotes (140). However, rRNA is one vitally important RNA that Nm drastically changes (141). The miRNA methyltransferase, Hen1, adds a methyl group to the most 3' nucleotide of miRNAs (142). In plants, 3'-end uridylation and 3'-to-5' exonuclease-mediated degradation of small RNAs are prevented by Hen1 (143). These results show the stabilizing effect of Nm on small RNAs via Hen1. Drosophila piRNAs also contain 2'-*O*-methylation at the 3' ends. Drosophila piRNA loses its Nm when piRNA methyltransferase, the Drosophila homolog of Arabidopsis Hen1, is lost (144). These results suggest that piRNAs may undergo Nm. In eukaryotes, fibrillarin, a conserved methyltransferase unit of a ribonucleoprotein complex directed by C/D box snoRNAs, places most Nm modifications (145). It has been shown that activation-induced cytidine deaminase-related snoRNA, aSNORD1C, interacts with 2'-O-methyltransferase fibrillarin to promote Nm (146).

m5C and m3C. m5C, a widespread RNA modification, is essential for regulating RNA fate and gene expression (147). m5C related enzymes, such as m5C methyltransferases [NOP2/sun (NSUN), DNA methyltransferase (DNMT) and TRDMT family members], demethylases [ten-eleven translocation (TET) family and ALKBH1] and binding proteins [YTHDF2, ALYREF and Y-box binding protein (YBX1)], dynamically regulate it (148,149). NSUN2 is an RNA methyltransferase that introduces m5C in nuclear-encoded tRNAs, mRNAs and miRNAs and has been associated with cell proliferation and differentiation. Pathogenic variations of mammalian NSUN2 have been connected to neurodevelopmental disorders (150). The nuclear-cytoplasmic shuttling of ALYREF, RNA-binding affinity and related mRNA export are all modulated by NSUN2 (151). YBX1 is essential for transcriptional control and RNA stabilization (152). TET2 facilitates the conversion of m5C to 5-hydroxymethylcytosine on tRNA and regulates the stability or processing of specific tRNA fragment classes (153).

m3C is widely distributed at position C32 of eukaryotic tRNAThr and tRNASer species (154). m3C, despite being less common, is frequently found in tRNAs, rRNAs and mRNAs (155). METTL6 in humans is a m3C methyltransferase that works with tRNAs, such as tRNASer (UGA) (155). In mouse stem cells, deletion of *Mettl6* causes alterations in RNA levels and ribosome occupancy in addition to decreased pluripotency (156). METTL8 has been proven to cause m3C in mRNA (157).

Other small RNA modifications

m7G. Human RNA modifications that are most common involve m7G (158). Numerous RNA molecules, including tRNAs, mRNAs, rRNAs and other non-coding RNAs, contain the m7G alteration (159). Several specific methyltransferases and m7G-binding proteins play a role in m7G regulation (159). The RNA methyltransferase, METTL1, catalyzes the m7G modification of tRNAs (160). METTL1/WDR4 mediates methylation within mRNA, while RNA guanine-7 methyltransferase (RNMT)/RNMT-activating mini-protein mediates methylation at the 5' cap (161). RNAs transcribed by RNA polymerase II in eukaryotic cells undergo alterations at the 5' end, termed the cap structure. The cap structure recruits eukaryotic translation initiation factor 4F, a crucial factor in translation initiation (162). A study revealed that preserving global proteome homeostasis, crucial for preventing early senescence, is primarily influenced by METTL1-mediated tRNA stability (163). A nuclear cap-binding protein complex is the other significant modulator of the cap structure (162).

m1A. An adenosine molecule with a methylated N1 position is known as m1A (164). Prokaryotic and eukaryotic RNAs display m1A methylation, a prevalent, abundant and conserved internal post-transcriptional modification particularly observed in higher eukaryotic cells (164). Long non-coding RNA (lncRNA), tRNA, mRNA and rRNA all contain m1A, a reversible modification controlled dynamically by writers, erasers and readers (165). The m1A modification is added to tRNA position 58 by the TRMT6-TRMT61A methyltransferase complex in humans (166). According to a study, YTHDF1-3 and YTHDC1 may directly bind to m1A in RNA, but not YTHDC2 (167). The YTHDF proteins, which are m6A readers, show specificity in identifying m1A-modified sequences during methylation (168).

Ψ. Ψ is an RNA modification found in various RNAs, including tRNA, rRNA, snRNA, snoRNA, mRNA and lncRNA (169-171). RNA-guided or stand-alone Ψ synthases synthesize Ψ, one of the most common RNA modifications (172). A recent study found that ALKBH3 mRNA is pseudouridylated, a process reliant on Ψ synthase 7 (PUS7), which enhances translation and slows gastric cancer growth (173). Crucially, ALKBH3 suppresses tumor growth in gastric cancer by carefully regulating the expression of PUS7 in tumor tissues (173). PUS7 inactivation in embryonic stem cells disrupts tRF-mediated translation regulation, increasing protein biosynthesis and leading to faulty germ layer specification. Thus, translation control is steered by Ψ-driven posttranscriptional programs to influence stem cell commitment in early development (174). Pseudouridylation can affect RNA splicing, processing and translation by making RNA stiffer and more stable (175).

5. Role of small RNAs in IBD and CRC

IBD

piRNA. It is critical to comprehend the role of piRNAs, a novel class of sncRNAs linked to several disorders in the last 10 years (176). A recent study indicates that piRNAs are not only found in the mammalian germline but are also expressed differently in different human tissues, and are linked to several diseases, including neurological, cardiovascular and urinary tract disorders (177). The roles of piRNAs in IBD are limited. However, piRNAs have been found to play certain roles in other diseases. For instance, putative piRNAs have been found in the mammalian brain, and they may have a similar role to piRNAs in the testes in silencing retrotransposons, which are vital contributors to the genomic variability in the brain that underlies adaptation, stress response and brain disease (178). It is documented that, in leukemia, has-piR-011186 upregulation accelerates cell cycle progression and reduces apoptosis (179). Ding *et al* (180) revealed that piR-823 activates Wnt signaling and induces cancer cell stemness in luminal subtype breast cancer cells by upregulating DNMT expression and encouraging DNA methylation of the *APC* gene. These are only a few of the numerous roles of piRNAs in other diseases; therefore, more studies focusing on IBD should be explored for therapeutic relevance.

tsRNA and snoRNA. Patients with IBD have a significantly higher isolation of *Aeromona*s species than patients without the illness. Downregulating cytoplasmic tRNA, small nuclear RNA and snoRNA is one of the ways *Aeromonas veronii* damages IECs (181), implying that these small RNAs may play a role in the pathogenesis of IBD. Although piRNA, tsRNA and snoRNA have been linked to other diseases such as Lewy body diseases (182), atrial fibrillation (183) and endometrial cancer (184), respectively, more research is needed to understand their pathogenesis in IBD.

miRNAs and the intestinal barrier in IBD. Maintaining the integrity of the intestinal mucosal barrier is essential for defending the epithelium of the intestine from pathogens and retaining commensal bacteria, which helps prevent

colitis (185). Occludins, claudins and zonula occludens (ZO) are tight junction proteins crucial for maintaining the integrity of the epithelial barrier (186). However, research has demonstrated that specific miRNAs harm the intestinal barrier, contributing to the pathophysiology of IBD. In this context, it has been discovered that miR-124 causes intestinal inflammation by blocking the aryl hydrocarbon receptor (AHR), which in turn affects the generation of cytokines that promote inflammation and advance the pathology of Crohn's disease (187). Guz *et al* (188) indicated that increased miRNA expression is associated with inflammation mediated by IBD and is inversely correlated with expression of the E-cadherin 1 (*CDH1)* gene, which suggests the function of epithelial-to-mesenchymal transition (EMT) in the development of IBD. E-cadherin is a crucial barrier in the colon that maintains organ balance and inhibits the growth of colon tumors (189). Consequently, increased miRNA expression and a reduction in *CDH1* may facilitate the transition to EMT. Similarly, miR301A is expressed at higher levels in IECs from patients with IBD who are actively ill, and CDH1 expression is downregulated by human IECs expressing transgenic miR301A (190). In other studies, lncRNAs have been found to either sequester miRNAs or inhibit them, contributing to the progression of IBD by disrupting the intestinal barrier. For instance, H19 lncRNA is a precursor for miR-675, which plays a crucial role in regulating the function of the intestinal epithelial barrier. Upregulation of H19 increases miR-675 cellular abundance, destabilizing and suppressing mRNAs encoding E-cadherin and ZO-1, ultimately causing membrane barrier malfunction (191). Additionally, lncRNA FBXL19 antisense RNA 1 diminishes the targeting of miR-339-3p to RAS homologous protein B and exacerbates intestinal epithelial barrier impairment in dextran sodium sulfate (DSS)-induced colitis in mice (192). Other lncRNA, including colon cancer-associated transcript-1, can damage the intestinal barrier by downregulating miR-185-3p (193).

By contrast, certain miRNAs have been shown to attenuate IEC injury or IBD, implying that miRNAs may play a dual role in IEC or IBD pathogenesis. miR-200b has been demonstrated to reduce tight junction damage and inhibit intestinal epithelial IL-8 release *in vitro* (194). Moreover, miR31, which is elevated in colon tissues from patients with UC or Crohn's disease, decreases the inflammatory reaction in the colon epithelium of mice by suppressing the production of signaling proteins (gp130) and receptors for inflammatory cytokines (IL7R and IL17RA) (195). In UC mice, miR-495 targets STAT3 and inhibits the Janus tyrosine kinase/STAT3 signaling pathway to improve intestinal mucosal barrier function (196). Research indicates that specific lncRNAs can bind to miRNAs, potentially preventing intestinal damage in IBD. For instance, PlncRNA1 (an lncRNA) binds to miR-34c, and PlncRNA1 upregulation appears to shield the intestinal epithelial barrier from damage. Nevertheless, upregulation of miR-34c counteracts the protective effects of PlncRNA1 on intestinal epithelial barrier function (197). This may suggest that PlncRNA1 binds to low expression of miR-34c to prevent damage to the intestinal barrier. Notably, the upregulation of miR-34c has been found to significantly alter the integrity and increase the permeability of the blood-tumor barrier (198). This further confirms the role of PlncRNA1 in binding to low miR-34c levels to prevent barrier damage.

miRNAs and immune response in IBD. Evidence supporting the regulatory function of miRNAs in the pathogenic pathways of several conditions encompassing IBD has been mounting in recent years, and based on these discoveries, miRNAs appear to be novel prospects for IBD treatment (199). miRNA, which functions as a post-transcriptional moderator of mRNA by binding to complementary regions inside mRNAs, participates in the intricate interplay between tumors and the immune system (200). Therefore, miRNAs are emerging as critical regulators of innate and adaptive immune responses, and aberrant immune system expression and function have been related to a number of human diseases, including inflammatory disorders such as IBD and cancer (201).

It has been documented that miR-132 and 223 inhibit FOXO3a to increase pro-inflammatory cytokine expression, making them essential mediators in the pathogenesis of IBD (202). Additionally, miR-124a can suppress AHR, disrupting intestinal inflammation and the intestinal barrier (203). One potential mechanism underlying inflammatory cell trafficking during colonic inflammation is the targeting of CXCL12β by the miR-141 pathway. Therefore, using miRNA precursors to inhibit colonic CXCL12β expression and prevent colonic immune cell recruitment is a potential strategy that could be useful for treating Crohn's disease (204). It has been shown that LPS-induced M1 macrophage polarization changes to M2 macrophage polarization by miR-98-5p knockdown, which reduces inflammation by upregulating tribbles homolog 1 (205), implying that miR-98-5p expression may control M1 macrophages to cause IBD. lncRNA has been demonstrated to modulate specific miRNAs, resulting in the stimulation of immune responses. For instance, Qiao *et al* (206) discovered that inhibiting lncRNA ANRIL can prevent UC by regulating the miR-323b-5p/TLR4/MyD88/NF-κB pathway, implying that the activation of lncRNA ANRIL may lead to the development of UC by regulating the miR-323b-5p/TLR4/MyD88/NF-κB pathway. The transcription-related factor, NF-κB, is a key modulator of inflammatory reactions and controls several facets of innate and adaptive immune responses (207).

The expression of nucleotide-binding oligomerization domain 2 and IL-12/IL-23p40 is inhibited by miR-10a, which also reduces inflammation in the inflammatory mucosa of patients with IBD and suppresses the Th1/Th17 cell immunological response (208). Another study has shown that miR-144/451 inhibits dendritic cell (DC) activation and improves DSS-induced colitis in mice by aiming specifically at the 3' UTR of interferon-regulatory factor 5 (209). It is also documented that miR-19b reduces the inflammatory response by decreasing the levels of suppressor of cytokine signaling 3, which modulates chemokine synthesis in IECs, thus preventing Crohn's disease pathogenesis (210). Additionally, miR-29a has been shown to suppress DSS-induced colitis. Real-time PCR assays have shown that miR-29 in $CD11c^+$ DCs suppress the synthesis of transforming growth factor-β (TGF-β), IL-23 subunits and IL-6 in DSS-treated mice (211). The regulation of miRNAs by lncRNA is crucial for reducing immune responses. For instance, Wang *et al* (212) discovered that increasing the expression of lncRNA maternally expressed 3 (MEG3) can reduce colonic ulceration in UC rats by upregulating

IL-10 expression through miR-98-5p sponging. Additionally, overexpression of lncRNA MEG3 in UC rat colons reduces oxidative stress, inflammation, apoptosis and pyroptosis (212). These results suggest that miRNAs may have dual roles in IBD immunological response regulation.

CRC

piRNA in CRC. PIWI-like proteins play a role in the development and advancement of cancer (213). piRNAs are widely distributed in human stomachs and may be crucial in the pathogenesis of gastric tumors (214); however, they have also been found in the biopsies of patients with CRC (16). Discovered >10 years ago, piRNAs, a subclass of sncRNAs, have garnered the interest of scientists due to their dual role in regulating gene expression in the cytoplasm and nucleus, and current research indicates that several types of human illnesses, including malignancies, are impacted by the aberrant expression of these sncRNAs (215). Additionally, globally, CRC is among the most common cancer types (216). The precise role and underlying processes of piRNAs in cancer, namely in CRC, remain incompletely elucidated (217). The proliferation, apoptosis, invasion and migration of cancer cells *in vitro* and *in vivo* are all known to be significantly influenced by the aberrant expression of piRNAs (217).

piR-823 is a recently identified marker for CRC that is highly effective in diagnosing the disease (218). It has also been discovered that piR-823 expression is significantly higher in colon cancer tissue than in surrounding tissues (219). Inhibiting piR-823 reduces the proliferation of cells, arrests cells in the G1 phase of the cell cycle and causes cell death in DLD-1 and HCT116 CRC cell lines; however, in the normal FHC colonic epithelial cell line, piR-823 overexpression increases cell proliferation (219). Notably, Cheng *et al* (220) found that gastric cancer tissues exhibit notably reduced expression of piR-823 compared with non-cancerous tissues. Cell proliferation is suppressed in gastric cancer cells following a rise in piR-823 levels, and the ability of piR-823 to decrease tumor growth has been validated by the outcomes of a xenograft-nude mouse model (220). Therefore, piR-823 may play different roles in cancer. Moreover, research shows that piRNA-18 expression is lower in CRC tissues and cancer cell lines compared with normal tissues and epithelial cells (216). Overexpression of piRNA-18 reduces cell proliferation, migration and invasiveness, arrests cells in the G1/S phase and decreases tumor volume and weight, suggesting that piRNA-18 may suppress CRC (216). Another study demonstrated the upregulation of piRNA-54265 in CRC relative to non-tumor tissues, and that elevated tumor or serum levels are closely connected to a lower patient survival rate (221). According to functional studies, piRNA-54265 binds the PIWIL2 protein, which is required for the PIWIL2/STAT3/p-SRC complex to form, thereby stimulating STAT3 signaling and encouraging the growth, metastasis and chemoresistance of CRC cells (221). These results indicate that the pathophysiology of CRC may involve piRNAs.

snoRNA in CRC. It has been found that snoRNAs can modify the fate of cells and the course of diseases, suggesting that they have great potential for managing human illnesses (15). There is a suggestion that dysregulation of snoRNAs demonstrate variable expression in different cancer types, stages and metastases, impacting patient prognosis and responsiveness to treatment (15). The crucial roles of snoRNAs in carcinogenesis have been recently identified; however, their specific contributions to CRC pathogenesis remain mostly unclear (222).

Notably, SNORA71A expression is elevated in CRC tissues and cells, and crucially, SNORA71A markedly aids in the invasion, migration and proliferation of CRC cells (223). Additionally, increased expression of SNORA15, SNORA41 and SNORD33 in patients with UC and CRC compared with healthy controls has been found, and these three snoRNAs may have a role in the development of CRC and the progression of the disease from chronic intestinal inflammation to malignant tumors (14). SNORA24 exerts its oncogenic role by facilitating the G1/S phase transition, enhancing cell proliferation, boosting colony formation and stimulating the growth of xenograft tumors (222). SNORA24 is elevated in several malignancies, including CRC (222). These results imply that snoRNAs may primarily influence the movement and growth of CRC cells. Hence, identifying the levels of expression and crucial processes can be advantageous in understanding prospective therapeutic approaches.

tsRNA in CRC. tsRNAs are a newly recognized class of sncRNAs that have a crucial function in cancer advancement (224); as a result, they might play a role in the etiology of CRC. In this regard, Lu *et al* (225) found that tRF-3022b, tRF-3030b and tRF-5008b exhibit an increasing trend in CRC tissues compared with nearby normal tissues. It was further discovered that a reduction in these three tRFs halts the progression of the CRC cell cycle and triggers cellular apoptosis. The mechanism of action of tRF-3022b is to bind to galectin 1 and macrophage migration inhibitory factor (MIF) in CRC cells, thereby reducing polarization through the regulation of MIF in M2 macrophages (225). This suggests that a rise in these tRFs may promote the CRC cell cycle and prevent apoptosis. Although there is evidence in the literature linking some tsRNAs to different types of cancer, research examining the connection between tsRNAs and cancer cell radiosensitivity has not yet been published (226). Recently, it has been discovered that radioresistant CRC cells have significantly reduced tRF-16-7X9PN5D expression. Mechanistically, tRF-16-7X9PN5D targets mitogen-activated protein kinase (MAPK)-interacting serine/threonine kinase-1, which enhances the ability of CRC cells to multiply, migrate, invade and acquire radiation resistance (226). Another study investigated the involvement of tRFs in EMT and its contribution to CRC development. It was found that several tsRNAs that are differently expressed are found during the EMT process in CRC (227). Therefore, high expression of tRF-VAL-TCA-002 and tRF-phe-GAA-031 in CRC tissues may have an essential function in the metastasis of CRC (227). *In vitro* and *in vivo* research has demonstrated that 5' tiRNA-His-GTG plays an oncogenic function in CRC, triggering cell death when targeted (228). The hypoxia-inducible factor 1 subunit α/ANG axis regulates the synthesis of 5' tiRNA-His-GTG, with large tumor suppressor kinase 2 being a key target for increasing pro-proliferation and the expression of anti-apoptosis genes (228). These results demonstrate the variable roles of tsRNA in CRC.

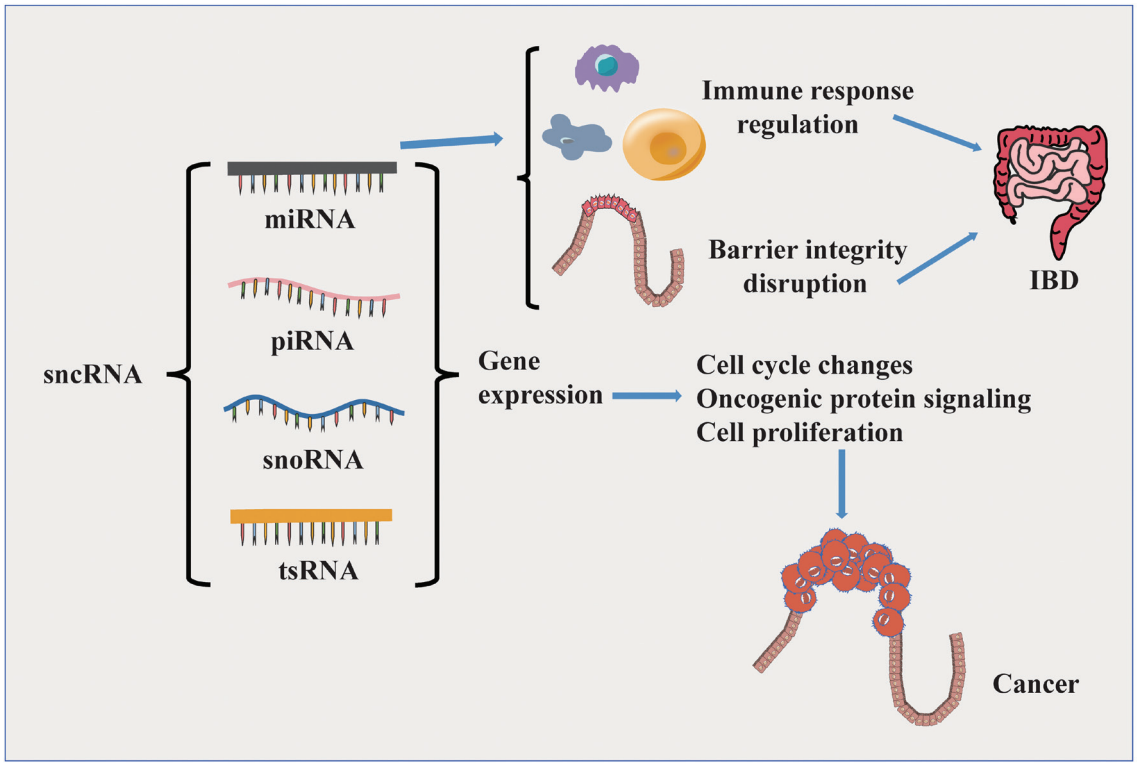

Figure 6. Summary of the roles of small RNAs in IBD/colorectal cancer pathogenesis. miRNAs influence the immune response and barrier integrity, resulting in IBD. At the same time, miRNA, piRNA, snoRNA and tsRNA can control gene expression, resulting in cell cycle alterations, cell proliferation and stimulation of the oncogenic signaling pathway, which leads to cancer. IBD, inflammatory bowel disease; miRNA, microRNA; piRNA, p-element-induced wimpy testis-interacting RNA; sncRNA, small non-coding RNAs; snoRNA, small nucleolar RNA; tsRNA, tRNA-derived small RNA.

miRNAs in CRC. miRNAs in circulation signify clinical pathologies such as inflammation and cancer development (229). Consequently, their function in cancer may provide patients with alternative therapeutic targets. In CRC, it has been documented that miR-27a-3p enhances the invasion and migration abilities of left-sided CRC (LSCC) and right-sided CRC (RSCC) cells by negatively controlling transcription factor 7-like 2 and TGF-β receptor type 2, respectively (230). Therefore, miR-27a-3p may be a promising molecular target for managing LSCC and RSCC (230). The upregulation of CRC cell growth and invasion may be indicated by circulating miR-762, which may also be correlated with Wnt/β-catenin signaling (231). Research suggests that miR-224 controls the 3'-UTR of the glycogen synthase kinase 3β (*GSK3β*) and secreted frizzled-related protein 2 (*SFRP2*) genes, thereby triggering nuclear translocation and Wnt/β-catenin signaling (232). The expression of GSK3β/SFRP2 is significantly suppressed by the ectopic overexpression of miR-224, which also increases the proliferation and invasion of CRC (232). It is also documented that patients with CRC have low levels of FOXF2 and high serum levels of miR-19a-3p, which are connected to age, sex, tumor size, lymph node metastasis, tumor-node metastasis stage and differentiation in patients with CRC. miR-19a-3p silencing and FOXF2 overexpression was also shown to inhibit cell invasion, migration, proliferation and EMT (233), implying that miR-19a-3p expression and FOXF2 suppression may lead to CRC growth. In another study, CRC tumor tissues exhibit increased oncogenic roles of miR-1915-3p and decreased tumor suppressor roles of miR-639, 641 and 3613-3p, with the MAPK signaling route being the most abundant pathway identified following Kyoto Encyclopedia of Genes and Genomes pathway analysis (234). miR-29a has shown potential as a tumor suppressor (235) and colitis inhibitor (211). Tang *et al* (236) found that increased expression of miR-29a facilitates CRC metastasis by modulating matrix metalloproteinase (MMP)2/E-cadherin via direct targeting of KLF4, demonstrating the potential of the miR-29a inhibitor as a new therapy against CRC metastases. These findings imply a dual role of miR-29a in CRC and IBD. Fig. 6 summarizes the involvement of small RNAs in IBD and CRC etiology.

6. Small RNAs as biomarkers in IBD and CRC

IBD

miRNA. miRNAs are essential for regular cell processes such as cell cycle regulation, apoptosis and differentiation. miRNAs target genes during embryonic and postnatal growth; nevertheless, their expression is disrupted in several pathological situations (237), including IBD and its complications. Therefore, miRNAs could be biomarkers for various clinical conditions (237). Elamir *et al* examined the miR-125b expression pattern in the serum of 210 patients with IBD and found that patients with UC and Crohn's disease had a much lower fold change of miR-125b than the controls (238). The receiver operating characteristic (ROC) curve analysis showed the diagnostic value of the marker as it differentiates between UC, Crohn's disease and control individuals (238). Another study also revealed that, while serum miR-25 can diagnose UC and Crohn's disease, serum miR-486 has the basis for clinical

utility in Crohn's disease diagnosis and could be used in the risk classification of IBD subgroups (239). miR-223 is elevated in the inflammatory and non-inflammatory tissues of patients with UC compared with tissues from healthy controls (240). Since the expression of this miRNA is independent of disease activity, it may be an effective biomarker for distinguishing between patients with UC and healthy individuals.

snoRNA and tsRNA. It is documented that SNORA15, SNORA41 and SNORD33 are upregulated in patients with UC and CRC compared with healthy controls and have a role in the progression of malignant tumors from chronic intestinal inflammation (14). As such, these snoRNAs might benefit patients with UC and CRC as potential diagnostic markers. Although tsRNAs have been identified as potential biomarkers in diseases such as liver cancer (241), pancreatic ductal adenocarcinoma (242) and potential therapeutic targets in keloid (243), few studies have examined tsRNAs and snoRNAs as biomarkers for IBD. Hence, more studies on tsRNAs and snoRNAs in IBD must be explored.

CRC

piRNA. Non-coding RNAs have been extensively studied over the past 20 years for several clinical disorders, including cancer (8). piRNAs, which regulate the activation of pathways and genes associated with the advancement of cancer of the GIT, have been identified as potential diagnostic and therapeutic biomarkers for the disease (244). Early CRC detection is the most critical element in determining its prognosis, thus developing an accurate screening test is a requirement (245), which will facilitate treatment alternatives.

It is documented that sera from patients with CRC consistently exhibit higher levels of piR-020619 and piR-020450 compared with controls (246). A prognostic panel utilizing these two piRNAs exhibited notable diagnostic precision for detecting CRC; therefore, serum piR-020619 and piR-020450 exhibit great promise as early detection biomarkers specific to CRC (246). Besides, the expression levels of piR-18849 and piR-19521 were shown to be elevated in 80 CRC tissues compared with the corresponding neighboring non-tumor tissues, and piR-18849 upregulation is also linked to increased lymph node metastasis; hence, piR-18849 and piR-19521 could potentially function as prognostic indicators for individuals with CRC (247). Mai *et al* (248) investigated the serum piR-54265 levels in 209 healthy individuals without cancer, 725 patients with CRC, 1,303 patients with different forms of digestive cancer and 192 patients with non-cancerous colorectal tumors. It was found that the levels of serum piR-54265 had a notable correlation with the diagnosis of CRC, suggesting its potential as a biomarker for clinical surveillance, early detection and CRC screening. In another study, overall survival is markedly reduced in patients with elevated piR-1245 expression, making it a potential oncogene and biomarker for CRC prognosis (249). Another investigation by Sabbah *et al* (245) indicated that piR-823 is expressed at notably higher levels in the serum and tissue of patients with CRC compared with controls, and for CRC, it can be used as a non-invasive diagnostic biomarker. Similarly, piR-823 in CRC has been investigated by Feng *et al* (250). It was revealed that piRNA-823 accelerated the course of CRC, presenting strong support for the growth of piRNA-823-based gene therapy for CRC and its potential application as a predictive biomarker. piR-24000 has also been identified as a diagnostic biomarker in CRC (16). Unfortunately, IBD piRNA biomarkers are scarce and more research is needed to aid clinical decision-making and treatment alternatives.

miRNA. miRNAs play a role in the growth and spread of CRC (251). In terms of diagnosis and treatment, molecular research is crucial (252). Numerous miRNAs possess the capacity to become novel, non-intrusive indicators for the prognosis and diagnosis of CRC, to direct surgical treatments and advance knowledge of the development of this cancer (253). Therefore, miRNAs from both invasive and non-invasive procedures may offer the potential for CRC diagnosis and prognosis. Zhang *et al* (254) have developed a seven-miRNA profile for CRC diagnosis using peripheral plasma. Compared with normal controls, the expression of these miRNA profiles (miR-103a-3p, miR-127-3p, miR-151a-5p, miR-17-5p, miR-181a-5p, miR-18a-5p and miR-18b-5p) was markedly higher in CRC. The areas under the ROC curves for the training, testing and external validation stages for the seven-miRNA signature were 0.762, 0.824 and 0.895, respectively, implying they may be used as diagnostic biomarkers for CRC. It is documented that patients with CRC have notably increased mean salivary expression levels of miR-92a and miR-29a compared with healthy controls (255). Regarding the miR-92a and miR-29a salivary biomarkers, the area under the ROC curves (AUCs) were shown to be 0.947 and 0.978, respectively, with increased sensitivity and specificity (255). Therefore, a precise diagnosis of CRC may be made using salivary miR-92a and miR-29a levels. Another study by Raonić *et al* (235) discovered a strong inverse correlation between Bcl-2 levels and miR-29a expression in patients with CRC. High miR-29a expression reduces the risk of distant metastasis and improves progression-free survival, indicating its potential as a prognostic biomarker for these patients. Hence, miR-29a could function as both a tumor suppressor and a promoter of CRC. Xu *e al* (256) revealed that, after exposure to *Fusobacterium nucleatum*, the METTL3/miR-4717-3p/MAP2K4 axis is a major driver of oncogenic progression and may be involved in the progression of *F. nucleatum*-related CRC. Consequently, miR-4717 may be an effective biomarker for diagnosis in patients infected with *F. nucleatum*.

The methylation of miR1, miR9, miR124 and miR137 in the rectal mucosa from patients with UC is notably higher compared with two other proximal areas in the colon, and significantly higher in those with cancer or dysplasia than in those with non-neoplastic UC mucosa (257). Hence, methylated miRNA biomarkers demonstrate strong potential for diagnosing patients with UC-associated CRC (UC-CRC) and can enhance the existing method of colonoscopic surveillance by identifying patients with a higher risk of neoplasia (257). Another study also found that miR-124 methylation in non-neoplastic rectal mucosa may be a valuable biomarker for recognizing individuals with childhood-onset UC at the highest risk of developing UC-CRC (258).

snoRNA. Research suggests that snoRNAs are involved in the development and carcinogenesis of cancer and may be helpful biomarkers for CRC, assisting with diagnosis and early intervention (259). SNORA42 upregulation increases

anoikis resistance, cell migration, invasion, proliferation and tumorigenicity both *in vitro* and *in vivo*, making it a potentially useful predictive biomarker for prognosis and recurrence in patients with CRC (260). Increased expression of SNORD1C has also been documented to be strongly correlated with poor prognosis and unfavorable outcomes in patients with CRC (7). Consequently, serum SNORD1C could be a non-invasive tumor indicator for diagnosing CRC (7). Similarly, Liu *et al* (261) found that SNORD1C expression is increased in CRC and is associated with a poor prognosis. SNORD1C enhances cancer cell stemness in CRC through the Wnt/β-catenin pathway and it may be a predictive biomarker for the aggressiveness and prognosis of this cancer. It has been revealed that SNORA5C and SNORD15B have carcinogenic effects in the genesis of CRC, indicating their potential as prognostic and diagnostic biomarkers for the disease (262). SNORA56 is markedly elevated in CRC tissue and plasma and is also a promising biomarker for CRC diagnosis and prognosis (263). By preventing the buildup of cellular peroxides, the SNORA56/28S rRNA/catalytic subunit of the glutamate cysteine ligase axis promotes the growth of CRC (263).

tsRNA. A growing body of research has recently examined the relationships between tsRNAs and tumors, demonstrating that tsRNAs can influence the biological behaviors of tumor cells, including apoptosis, metastasis and proliferation, by modifying RNA transcription, protein translation or post-transcriptional regulation (264). It has been observed that tsRNAs have both tumor suppressor and oncogenic properties and that these functions are crucial for the initiation and spread of different types of cancer (265). Furthermore, tsRNAs are extensively dispersed and stable in expression, providing them with a wide range of application prospects in tumor diagnosis and prognosis prediction, and they are anticipated to emerge as novel biomarkers (264). Consequently, the utilization of tsRNAs as biomarkers for therapeutic objectives might be required. Differential expression of tsRNAs has been observed during CRC EMT (227). CRC tissues have greater expression levels of tRF-phe-GAA-031 and tRF-VAL-TCA-002, which may be significant factors in CRC metastasis and beneficial indicators for the diagnosis and prognosis of CRC (227). Wang *et al* (266) revealed that 5□tiRNA-Pro-TGG may be a target for the prompt diagnosis of sessile serrated lesions and the therapy of CRC caused by the serrated pathway. Tsiakanikas *et al* (267) also examined the predictive usefulness of 5'-tiRNA-Pro-TGG levels in CRC and found a poor disease-free survival and overall survival in patients with CRC and elevated 5'-tiRNA-Pro-TGG levels. Most notably, proven medical prognosticator integration in a multiparametric Cox regression model revealed that 5'-tiRNA-Pro-TGG expression has independent prognostic relevance. These observations present notable evidence that piRNA, tsRNA, miRNA and snoRNA are potential biomarkers for IBD and CRC (Table I) (7,16,227,238,239, 245-249,254-257,260,262,266,267).

Small RNAs as biomarkers for other digestive system diseases. Table II (241,268-277) summarizes the application of small RNAs as biomarkers in other digestive system diseases, including the liver, pancreas, gastric and esophagus.

7. Role of small RNAs in immuno-oncology

Numerous years of oncological clinical experience have shown that cancer immunotherapy offers extraordinary therapeutic benefits (278). Immunotherapy has revolutionized cancer treatment by utilizing the power of the immune system to kill tumors (279). One important tool in the fight against cancer is immune checkpoint blockade therapy (280). Therefore, checkpoint biology-based immunotherapies hold significant potential for future cancer treatment (280). A major advancement in the field of cancer immunotherapy has been made with the identification of immunological checkpoint proteins, such as cytotoxic tumor lymphocyte antigen 4 (CTLA-4) and programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) (281). PD-1 and PD-L1 are crucial molecules for regulating immune responses. When PD-L1 binds to PD-1 on active T cells, it initiates signaling pathways that might cause T cell anergy or death, which helps the immune system evade tumors (282). Notably, studies have shown that miRNA may target PD-L1/PD-1 on activated T cells to aid in anticancer treatment responses in CRC and IBD.

miRNA and immune checkpoint therapy in CRC. miRNAs have been found to inhibit immunological checkpoints in CRC and enhance T cell-mediated anticancer responses. For instance, Roshani Asl *et al* (283) found that miR-124 can suppress PD-L1 expression in CRC cells, which may improve the T cell-mediated anticancer response. In addition, miR-124 significantly reverses cancer characteristics (proliferation, stemness, migration and invasion) in CRC cells by reducing STAT3 signaling activity and altering its downstream targets, indicating its potential tumor-suppressive effect. Additionally, exosomal miR-124 from bone marrow mesenchymal stromal cells (BMMSCs) enhances the PD-1 blocking therapy response and inhibits tumor growth in ovarian cancer immunotherapy (284). The study suggests a potential therapeutic method for enhancing immune checkpoint blockade therapy using exosomes from BMMSCs carrying miR-124 (284). Another study by Jin *et al* (285) found that polydatin modulates the miR-382/PD-L1 axis to suppress CRC cell growth and induce apoptosis. The study confirmed that miR-382 directly targets PD-L1 and that polydatin could inhibit PD-L1 expression by increasing miR-382. These results demonstrate the role of miRNAs in immune checkpoints in CRC preclinical studies.

In a clinical study, Jiang *et al* (286) discovered that miR-140-3p, a tumor suppressor in CRC, directly targets PD-L1 and inactivates the PI3K/AKT pathway, suggesting it is a potential target for CRC diagnosis and treatment. Overexpression of miR-140-3p inhibits proliferation, migration and invasion while inducing apoptosis in CRC cells. A different study by Chen *et al* (287) found that dexmedetomidine (DEX) partially increases miR-140-3p levels in RLE-6TN (alveolar epithelial) cells, which helps suppress PD-L1 expression. DEX also inactivates the JNK/Bnip3 pathway, which reduces inflammation and alveolar type II cell damage. Additionally, Chen *et al* (288) found that the expression of miR-93-5p decreases in CRC tissues while PD-L1 increases. The expression level of miR-93-5p was higher in patients with PD-L1-negative CRC than those with

Table I. Potential small RNA biomarkers for inflammatory bowel disease and CRC.

A, piRNA

First author, year	Name and expression	Sample	Type of disease	Potential diagnosis	AUC	Potential prognosis parameter	(Refs.)
Wang *et al*, 2020	piR-020619↑, piR-020450↑	Serum	CRC	√	0.863 (small-size CRC), 0.839 (early-stage)	-	(246)
Yin *et al*, 2019	piR-19521↑, piR-18849↑	CRC and adjacent non-tumor tissues	CRC	-	-	√ Poor degree of differentiation	(247)
Mai *et al*, 2020	piR-54265↑	Serum	CRC	√	0.896	-	(248)
Weng *et al*, 2018	piR-1245↑	Cancer tissues and paired normal mucosa	CRC	-	-	√ Shorter OS	(249)
Sabbah *et al*, 2021	piR-823↑	Serum and tissues of CRC and comparable healthy tissues	CRC	√	0.933	-	(245)
Iyer *et al*, 2020	piR-24000↑	Tumor and adjacent normal tissue	CRC	√	0.8175	-	(16)

B, miRNA

First author, year	Name and expression	Sample	Type of disease	Potential diagnosis	AUC	Potential prognosis parameter	(Refs.)
Elamir *et al*, 2022	miR-125b↓	Blood (serum)	CD, UC 1 (UC), 0.677 (CD, UC)	√	0.886 (CD),	-	(238)
Abdelazim *et al*, 2023	miR-486[a]↑	Serum	CD, UC	√	0.945	-	(239)
Toiyama *et al*, 2017	miR1↑, miR9↑, miR124↑, miR137↑	Colorectal tissue specimens	UC-CRC	√	0.92, 0.94, 0.98, 0.98	-	(257)
Zhang *et al*, 2019	miR-103a-3p↑, miR-127-3p↑, miR-151a-5p↑, miR-17-5p↑, miR-181a-5p↑, miR-18a-5p↑, miR-18b-5p↑	Plasma exosomes and CRC tissues	CRC	√	0.762, 0.824 and 0.895 (training, testing and external validation)	-	(254)
Xu *et al*, 2022	miR-4717↑	Tumor and paired paracancerous tissue	CRC	√	0.737/73.7%	-	(256)
Koopaie *et al*, 2024	miR-92a↑, miR-29a↑	Saliva	CRC	√	0.947, 0.978	-	(255)

Table I. Continued.

First author, year	Name and expression	Sample	Type of disease	Potential diagnosis	AUC	Potential prognosis parameter	(Refs.)
C, snoRNA							
Okugawa *et al*, 2017	SNORA42↑	Colorectal tissues, colon cancer cell lines	CRC	√	0.75	√ Poor OS	(260)
Liu *et al*, 2021	SNORD1C↑	Serum	CRC	√	0.838[b]	-	(7)
Shen *et al*, 2022	SNORD15B↑, SNORA5C↑	CRC tissues and adjacent normal mucosa tissue	CRC	√	0.83, 0.86	√ Decreases 5-year OS	(262)
D, tsRNA							
Wang *et al*, 2023	tiRNA-1:33-TGG-1 (5'-tiRNA-Pro-TGG)↑	SSL tissues and adjacent normal tissues	CRC	√	-	-	(266)
Tsiakanikas *et al*, 2022	5′-tiRNA-Pro-TGG↓	CRC and non-CRC tissues	CRC	-	-	√ poor DFS and OS (high 5′-tiRNA-Pro-TGG)	(267)
Chen *et al*, 2022	tRF-Phe-GAA-031↑, tRF-Val-TCA-002↑	CRC tumor and adjacent non-tumor, CRC cells	CRC	√	0.7554, 0.7313	√ Poor OS	(227)

[a]No change in UC. [b]Combined with carcinoembryonic antigen. AUC, area under the receiver operating characteristic curve; CD, Crohn's disease; CRC, colorectal cancer; DFS, disease-free survival; miR/miRNA, microRNA; OS, overall survival; piR/piRNA, p-element-induced wimpy testis-interacting RNA; SNORA, box H/ACA snoRNA; SNORD, box C/D snoRNA; SSL, sessile serrated lesions; tRF, tRNA-derived fragment; UC, ulcerative colitis; UC-CRC, UC-associated colorectal cancer; snoRNA, small nucleolar RNA; tsRNA, tRNA-derived small RNA.

Table II. Small RNAs as biomarkers for other digestive system diseases.

First author, year	Name and expression	Sample	Type of disease	Potential diagnosis	AUC	Potential prognosis parameter	(Refs.)
A, tsRNA							
Xie *et al*, 2023	tRF-18-79MP9P04↓	Gastric mucosa, plasma	Gastric cancer	√	0.714 (EGC), 0.704 (AGC)	-	(268)
Zhu *et al*, 2019	tRNA-ValTAC-3↑, tRNA-GlyTCC-5↑, tRNA-ValAAC-5↑, tRNA-GluCTC-5↑	Plasma exosomes	Liver cancer	√	-	-	(241)
Jin *et al*, 2021	tRF-Pro-AGG-004↑, tRF-Leu-CAG-002↑	Serum	Pancreatic cancer	√	Training (0.88 for tRF-Pro-AGG-004, 0.93 for tRF-Leu-CAG-002); validation (0.90 for tRF-Pro-AGG-004, 0.78 for tRF-Leu-CAG-002)	√ Worse prognosis	(269)
B, snoRNA							
Liu *et al*, 2018	SNORA21↑	Gastric cancer and adjacent normal tissues	Gastric cancer	-	-	√ Poor DFS and OS	(270)
Ding *et al*, 2020	SNORA71A↓	Hepatocellular carcinoma cell lines and tissues	Hepatocellular carcinoma	-	-	√ Poor OS	(271)
Kitagawa *et al*, 2019	SNORA74A↑, ↑SNORA25	Serum	Pancreatic ductal adenocarcinoma	√	>0.9 (0.909 for SNORA74A, 0.903 for SNORA25)	-	(272)
C, miRNA							
Kumata *et al*, 2018	miR-23b↓	Plasma exosome	Gastric cancer	√		√ Worse OS	(273)
Moshiri *et al*, 2018	miR-101-3p↑, miR-106b-3p↑, miR-1246↑	Plasma and serum	Hepatocellular carcinoma	√	0.71, 0.96, 0.83	-	(274)
Huang *et al*, 2023	miR-4488↑	Plasma	Squamous cell carcinoma of the esophagus	√	0.8076	-	(275)

Table II. Continued.

D, piRNA							
First author, year	Name and expression	Sample	Type of disease	Potential diagnosis	AUC	Potential prognosis parameter	(Refs.)
Zhou *et al*, 2020	piR-1245↑	Gastric juice	Gastric cancer	√	0.885	√Poorer OS and PFS	(276)
Rui *et al*, 2023	piR-1029↑, piR-15254↑, piR-35395↑, piR-32132↑, piR-43597↑	Serum exosome	Hepatocellular carcinoma	√	Training AUC =0.986 (for all piRNAs), Validation AUC =0.981 (for all piRNA)	-	(277)

AGC, advanced gastric cancer; AUC, area under the receiver operating characteristic curve; EGC, early gastric cancer; miR/miRNA, microRNA; OS, overall survival; PFS, progression-free survival; piR/piRNA, p-element-induced wimpy testis-interacting RNA; SNORA, box H/ACA snoRNA; tRF, tRNA-derived fragment; UC, ulcerative colitis; snoRNA, small nucleolar RNA; tsRNA, tRNA-derived small RNA.

PD-L1-positive CRC. Furthermore, the study found that miR-93-5p targets *PD-L1* to downregulate MMP1, MMP2 and MMP9, thereby inhibiting motility, invasion and immune evasion of CRC cells. An increase in miR-93-5p may lead to a decrease in PD-L1. In patients with breast cancer, miR-93-5p has been found to inhibit cell proliferation, migration and invasion as well as cell cycle progression (289). The study further found that miR-93-5p targets PD-L1/Cyclin D1 in breast cancer to control carcinogenesis and tumor immunity.

Multiple miRNAs have been demonstrated to target PD-L1 to prevent tumorigenesis (290-292). Nevertheless, non-coding RNAs such as LINC00460 (293) have been found to act as molecular sponges for miR-186-3p, promoting PD-L1 expression and facilitating tumorigenesis in CRC. Similarly, circular_0000052 (294) has been found to bind to miR-382-3p, thereby increasing PD-L1 expression and enhancing cell aggression in head and neck squamous cell carcinoma. Small RNAs such as piRNA, tsRNA and snoRNA may require further investigation to understand their role in other tumor immune checkpoints in CRC.

miRNA and immune checkpoint therapy in IBD. Immune checkpoint inhibitors (ICIs) can improve survival but may also cause immune-related adverse events (irAEs), such as irAE-colitis, which hinders the progression of immune checkpoint treatment (295,296). Blocking TNF-α and modifying the gut flora are useful approaches to combat this (296). A study by Grover *et al* (297) revealed that patients with pre-existing colitis receiving an ICI for a solid tumor developed enterocolitis. Anti-TNF medication was administered to a few patients. As a result, ICI therapy was stopped in all patients. The study suggests that ICIs may be effective in treating patients with cancer and IBD or microscopic colitis; however, patients should be continuously monitored for possible flare-ups of enterocolitis, and patients with pre-existing colitis should utilize the immune checkpoint combination with caution. Notably, Abu-Sbeih *et al* (298) also found that patients with preexisting IBD are more likely to experience severe gastrointestinal side effects when receiving ICIs. Thus, small RNAs that show increased expression upon anti-TNF treatment may be combined with ICIs to enhance outcomes in immunotherapy for IBD. For instance, co-administration of surrogate anti-CTLA-4 and anti-PD-1 monoclonal antibodies to mice improves transplantable cancer models but worsens autoimmune colitis (299). Notably, colitis is improved and antitumor activity is increased in mice treated concurrently with therapeutically accessible TNF inhibitors and combination CTLA-4 and PD-1 immunotherapy (299). Although this study did not investigate the role of miRNA, there is an inverse correlation between TNFα and miR-374a-5p (300). Increased expression of miR-374a-5p modulates macrophage-induced inflammation by inhibiting proinflammatory mediators and reducing the capacity of monocytes to migrate and activate T cells (300). Therefore, miRNAs that block TNF may be feasible in combination treatment with CTLA-4 and PD-1 inhibitors. Although particular miRNA regulation in IBD immunotherapy is limited, further studies are needed to explore their roles in IBD immunotherapy. Additionally, investigations on ICIs using other small RNAs should be conducted.

8. Nanoparticle-mediated treatment approach in IBD and CRC

The instability of medications in the GIT, the inability to target disease tissues effectively and significant side effects make it impossible to achieve treatment involving oral nucleic acids. Advances in nanotechnology have produced polymeric nanoparticles, a promising framework for encapsulating different natural active small molecules (NASMs) (301). This enables the delivery of oral-loaded NASMs to specific tissues or cells, enhancing their stability and bioavailability while circumventing drug delivery obstacles (301). Nanoparticles can be classified as polymer-based, lipid-based or a lipid-polymer hybrid, depending on the type of delivery vehicle used to transport them (302). It has been discovered that extracellular vesicles and nanoparticle delivery systems can transport these nucleic acids to the intended tissues due to their diverse properties. For instance, Gao *et al* (303) found that colon tissues tend to absorb and retain sodium alginate (SA)@ metal-organic framework (MOF)-siRNATNFα. The oral delivery of the SA@MOF-siRNATNFα engineered particle markedly slowed down the development of colitis. After entering the cell through endocytosis, SA@MOF-siRNATNFα released the siRNA at the targeted location. Treated mice did not considerably lose weight or develop diarrhea or bloody stools, improving the MOF-siRNA distribution to the colon (303). Additionally, applying extracellular vesicles from bovine milk (MEVs) loaded with anti-TNFα siRNA decreases inflammation in an IBD rat model (19). The oral administration of anti-TNFα siRNA enters intestinal tissues (intestinal epithelium), facilitating the release of siRNA to prevent TNFα and reduce inflammation. MEVs may guide the development of synthetic systems for treatment applications as they function as safe and natural systems for nucleic acid therapy in oral treatments (19). In comparison to intravenous injection, the most effective fluorinated (F) 3-nanocapsules (NCs) exhibit a 20.4% oral bioavailability due to their superior mucus penetration and intestinal transport capacities, all without compromising the intestinal tight junction (304). The NCs can break inside target cells to cause NC dissociation and siRNA release, increasing TNF-α silencing effectiveness. This shell structure, which is disulfide-cross-linked, makes the NCs stable in the GI tract. Therefore, in mice with both chronic and acute inflammation models, F3-NCs administered orally have significant anti-inflammatory effects and result in effective TNF-α suppression (304).

Moreover, Xu *et al* (305) found that the combination of miR-375 and 5-fluorouracil (5-FU)/lipid-coated calcium carbonate nanoparticles show a markedly more significant therapeutic benefit than the individual therapies in murine subcutaneous xenografts established with HCT116 cells. In tumor tissues from oxaliplatin (OXA)-resistant patients, asporin (ASPN) is highly expressed and is strongly associated with a poor prognosis in CRC (306). A study discovered that a nanoparticle-based co-delivery system [PEG- and OXA-modified PAMAM (PPO)-siASPN] effectively suppresses the expression of ASPN for synergistic antitumor activity both *in vitro* and *in vivo* while also facilitating the intracellular delivery of OXA through enhanced cellular uptake (306).

Despite the effectiveness of siRNA distribution by nanoparticles, there are still significant challenges to overcome. A recent study by Huang *et al* (306) suggests that PPO-siASPN nanoparticles may have some systemic toxicity, but the level of toxicity is very minimal. Moreover, Gao *et al* (303) used siRNA-loaded MOF encapsulated in SA particles to overcome the barriers in the oral process; however, this method only improved siRNA treatment. Although 84.12% of the siRNA was released from MOF-siRNA, only 52.3% of the intact siRNA in the SA@MOF siRNA was found after passing through the gastric juice and small intestine fluid. This suggests that a lower amount may reach the inflammatory location in the colon. The main obstacle to siRNA-mediated gene modification in the intestinal epithelium may be uniform delivery throughout the intestines (307). Another study by Wei *et al* (304) found that the oral delivery of siRNA using fluorinated, small-sized nanocapsules (~30 nm) achieves only 20.4% oral bioavailability compared with intravenous injection. This may suggest that only 20.4% of siRNA reaches the bloodstream, possibly due to the harsh conditions in the GIT.

Exosomes are drawing significant research attention as potentially new IBD therapeutic options due to their unique biological properties (308). Exosomes are 40-100 nm-sized membrane vesicles released from the late endosomal cellular compartments of various cell types. Exosomes are found in several bodily fluids, such as saliva, amniotic fluid, urine, plasma and malignant ascites. Exosomes contain proteins, microRNAs and mRNAs (exosome shuttle RNA), which may provide a novel diagnostic platform (309). Cells generate exosomes through the process of exocytosis. Target cells then take up these particles and transfer biological information between adjacent or distant cells (310). Thus, exosomes might mitigate IBD by transferring small RNAs to target cells. For instance, exosomal miR-539-5p produced by bone MSCs inhibits the course of IBD by suppressing pyroptosis through the nucleotide-binding domain-like receptor family member pyrin domain-containing protein 3 (NLRP3)/caspase-1 signaling (311). Additionally, exosomal miR-590-3p from M2 macrophages targets large tumor suppressor homolog Ser/Thr kinase 1 and activates Yes-associated protein/β-catenin-regulated transcription to suppress inflammatory signals and promote epithelial regeneration (312). In a mostly exosome-dependent manner, macrophages delivered extracellular miR-590-3p into epithelial cells, aiding mucosal healing following DSS damage (312). This could potentially open up new therapeutic opportunities for UC (312).

One reported novel mechanism of CRC treatment resistance is the exosomal transfer of non-coding RNAs (313). Although still in its early stages, this area of research has shown great potential for identifying new biomarkers for monitoring therapy and reversing drug desensitization (313). Notably, combining miR-21 inhibitor oligonucleotide and 5-FU in engineered exosomes successfully reversed drug resistance in 5-FU-resistant colon cancer cells, increasing cytotoxicity (314). These studies indicate that engineering exosomes and other extracellular vesicles to deliver RNAs holds great promise in treating IBD and CRC and requires further exploration.

Exogenous therapeutic miRNA-enriched extracellular vesicles are effective delivery vehicles, and their cell-based

applications are rapidly expanding (315). Studies have used exosomes as extracellular vesicles to deliver miRNA in the inflamed colon (311,312). Lipofectamine™ 3000 was used in these studies to introduce miRNAs to cells *in vitro*. The delivery strategies for miRNA nanoparticles in treating IBD remain largely unknown (316). At present, siRNA delivery system protocols form the basis for miRNA delivery system development (316). Therefore, potential challenges in delivering miRNA to cells may include the success rate of introduction.

Although engineered exosomes may efficiently carry 5-FU and miR-21 inhibitors to cancer cells, the tagged GFP dye coupled to LAMP2 is not detectable in the exosome, THLG-EXO, during *in vivo* research on the THLG-EXO pharmacokinetics. Thus, future studies are needed to seek a properly detectable signaling protein to label exosomes for *in vivo* detection (314). The increased diameter of exosomes following electroporation, which has been suggested to be induced by nucleic acid aggregation in the study by Liang *et al* (314), may also pose a difficulty. These obstacles may impact the effectiveness of translation into the therapeutic arena. Furthermore, few recent clinical trial findings or advances in nanoparticle)-based miRNA delivery exist. Thus, it is impossible to demonstrate the effectiveness and potential of these strategies in real-life scenarios.

9. Limitations of the study of IBD and CRC

Research on IBD (238-240) and CRC (7,248,254,266,317) has utilized small sample sizes for diagnostics, prognostics and clinical surveillance. Thus, larger sample sizes are proposed for further validation of the use of small RNAs as diagnostic or prognostic markers. The larger sample sizes may help increase statistical diagnostic power by reducing standard errors and increasing precision. A previous study used insufficient tissue samples for deep sequencing, potentially leading to the exclusion of several notable piRNAs due to the lack of available samples (247). The study only employed three pairs of CRC samples for deep sequencing to ascertain the expression of piRNAs in CRC and nearby non-tumor tissues. In addition, the mechanisms of piRNAs and snoRNAs are not yet well understood based on current research (247,248,262). As a result, addressing the specific processes of these small RNAs may aid in understanding the etiology of CRC. Another drawback noted in a study by Toiyama *et al* (257) is the use of miRNAs only linked to aging and cancer in UC-CRC. However, future research involving a more comprehensive, objective genome-wide study may uncover more methylation locations to evaluate UC-CRC risk (257). Studies (241,247,266) have not reported AUC values for the diagnostic ability of small RNAs, despite their potential use as biomarkers for cancer/IBD. More studies should include AUC values in future studies to better understand these potential biomarkers.

10. Conclusions and future directions

IBD, encompassing Crohn's disease and UC, is a persistent inflammatory ailment associated with an increased risk of CRC. Small RNAs have been linked to various illnesses, including IBD and CRC. These small RNAs also serve as potential biomarkers for these diseases, offering a cutting-edge approach for investigating possible treatments. Treatments involving oral nucleic acid are now achievable due to the nanoparticle or exosome delivery system of these medications, which effectively targets disease tissues by overcoming the instability of the GIT, resulting in an effective outcome.

Future research should investigate the pathophysiology of additional small RNAs, including tsRNAs, piRNAs and snoRNAs, in IBD for possible therapeutic applications. According to the present review, piRNAs, tsRNAs and snoRNAs play little function in IBD; nevertheless, Lee *et al* (181) have revealed a relationship between several small RNAs and *Aeromonas* species in IBD. The downregulation of tRNA, snRNA and snoRNAs in human IECs is one of the unique *Aeromonas veronii*-related pathways among those that have been found (181). Therefore, modulating the gut bacteria with therapies such as antibiotics and other biological treatments may help prevent small RNA-induced IBD. Although the majority of strains of *Aeromonas* species are responsive to co-trimoxazole, ciprofloxacin, chloramphenicol and aminoglycosides, amoxycillin/clavulanate and acylureidopenicillins have variable action (318). This might be a new area that researchers can examine to determine the precise processes by which these medicines regulate gut flora and their relationship with these small RNAs. Additionally, the potential combination of small RNA-based therapies with other treatment modalities should be explored for improved outcomes. This may be a groundbreaking therapy for managing CRC. For instance, studies have shown the potential of an effective treatment combination of CRC medications (including 5-FU and oxaliplatin) and small RNA or its inhibitors using nanoparticles (305,306,314). These treatments can overcome chemoresistance in CRC. Other CRC chemotherapeutic drugs include cisplatin, vincristine, irinotecan and doxorubicin. However, these drugs experience resistance that can lead to chemotherapy failure or serve as a barrier to cancer therapy (319-323). The combination of small RNAs and doxorubicin has shown promise in treating chemoresistance in breast cancer and its generated drug-resistant cells via a nanoparticle delivery strategy. For instance, Chen *et al* discovered that transfecting multidrug resistance (MDR)-1 siRNA-doxorubicin-silica into MCF-7/MDR cells (a breast cancer cell line and its derived drug-resistant cells) may improve doxorubicin sensitivity, resulting in greater chemotherapeutic cytotoxicity (324). Liu *et al* (325) recently discovered that endogenous and exosomal miR-7-5p enhance therapeutic effectiveness of everolimus by inhibiting non-small cell lung cancer proliferation, migration and metastasis *in vitro* and *in vivo*. These results suggest that nanoparticle administration of coupled RNAs and anticancer medicines could prevent cancer cell proliferation and decrease chemotherapy resistance. Additionally, Koopaie *et al* (255) suggest exploring statistical analysis and machine learning as cost-effective, non-invasive techniques for CRC. Statistical and machine-learning techniques can be developed using saliva mRNA levels, demographic data and clinical characteristics (255). This may reduce the risk of trauma and bleeding associated with invasive procedures. It is also advisable to utilize advanced technology on small RNAs with ambiguous processes to enhance the comprehension of their mechanisms.

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Authors' contributions

Conceptualization was conducted by WQ and YL; funding acquisition and project administration was conducted by FM and DKWO; visualization was conducted by YX; writing the original draft was conducted by FAA and WQ; review and editing the manuscript was conducted by DKWO and FM. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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