



Review

Expression and Function of miR-155 in Diseases of the Gastrointestinal Tract

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Abstract: MicroRNAs (miRNAs) are a type of small noncoding RNA that can regulate the expression of target genes under physiological and pathophysiological conditions. miR-155 is a multifunctional miRNA with inflammation-related and oncogenic roles. In particular, the dysregulation of miR-155 has been strongly implicated in *Helicobacter pylori*-related gastric disease, inflammatory bowel disease, and colorectal cancer in addition to being involved in molecular changes of important targets and signaling pathways. This review focuses on the expression and function of miR-155 during inflammation and carcinogenesis and its potential use as an effective therapeutic target for certain gastrointestinal diseases.

Keywords: miR-155; *H. Pylori*; inflammatory bowel disease; colorectal cancer

1. Introduction

MicroRNAs (miRNAs) are an abundant class of small noncoding RNAs that mostly down-regulate protein expression by either inducing mRNA degradation or suppressing protein synthesis. In 1993, the unique function of miRNAs was revealed for the first time in *Caenorhabditis elegans* by Lee *et al.* [1], who demonstrated regulation of *lin-14* translation via an antisense RNA–RNA interaction. The precise structure of miRNAs determines their function. The biogenesis of miRNAs is a complex multi-step process involving many posttranscriptional modifications in the nucleus and cytoplasm. First, RNA polymerase II transcribes *miR* genes, generating primary miRNA (pri-miRNA). Next, pri-miRNA cleaves to the miRNA precursor (pre-miRNA) via the RNase III enzyme Drosha and the double-stranded-RNA-binding protein DGCR8 [2]. The cytoplasmic endonuclease Dicer cleaves the pre-miRNA stem-loop forming a 21–24 bp duplex miRNA. Next, one strand is loaded into the RNA-induced silencing complex (RISC) containing Argonaute (AGO) proteins [3–5]. The mature miRNA in the RISC then binds the 3′ Untranslated Regions (3′UTR) of the target mRNAs and blocks their translation. Downstream target mRNAs of miRNAs play important roles in biological processes such as proliferation, differentiation, cellular migration, and apoptosis. Numerous reports indicate that miRNAs are associated with the posttranscriptional regulation of many proteins that are involved in numerous physiological and pathological processes [6,7], such as hematopoietic lineage differentiation, immunity, inflammation, cancer, and cardiovascular diseases [8].

MiR-155, an evolutionarily well-conserved miRNA that is mainly expressed in the thymus and spleen, is minimally detected in other tissues under normal physiological conditions. Transcription of miR-155 may be regulated by the activator protein-1 (AP-1) complex [9] and the nuclear factor- κ B (NF- κ B) transcription complex [10]. Target genes that are regulated by miR-155 include approximately 140 genes that encode for immunomodulatory proteins, tumor-suppressor proteins, and inflammatory-related proteins. Hence, ectopic miR-155 is often associated with specific

disorders, including cardiovascular diseases, inflammation, and cancer [8]. Unlike the other miRNAs, miR-155 has been widely studied in the immune system under conditions of normal and abnormal immune responses and hematologic malignancies. In the gastrointestinal tract, abnormal miR-155 expression can be detected during *Helicobacter pylori* infection, and increased expression is observed in patients with inflammatory bowel disease (IBD) and colorectal cancer (CRC) [11–13]. However, miR-155-deficient mice not protected by immunization to *S. typhimurium* failed to produce significant levels of these cytokines [14]. Similarly, miR-155 is also essential for T-cell-mediated control of *H. pylori* infection [15]. Therefore, miR-155 may have unique functions in the immune-mediated process of certain gastrointestinal diseases.

2. Inflammation and Cancer

The inflammatory response is a complex process involving the induction of several inflammation-related genes and the activation of the immune system, which acts to clear pathogens and avoid pathological consequences. It is well-known that miR-155, as an important regulator, performs multiple functions in the immune system and is also required for normal immune function [14]. miR-155 expression in both myeloid and lymphoid cells following their activation is greatly increased in response to corresponding stimulation [9,16]. According to numerous recent studies, PU.1, AID, c-Maf, Bach1, Sla, Cutl1, Csf1r, Jarid2, Cebp, Arntl, Hif1 α , Picalm, TAB2, SOCS1, SHIP-1, Rab6a, and others may act as functional targets of miR-155 in myeloid and lymphoid cells [14,17–23]. miR-155 has been identified and characterized as a component of the primary macrophage response to different types of inflammatory mediators such as bacterial lipopolysaccharide (LPS), interferon- β (IFN- β), polyriboinosinic-polyribocytidylic acid (poly IC), and tumor necrosis factor- α (TNF- α) [9]. Moreover, up-regulation of miR-155 is often associated with increased cytokine release during the inflammatory process [24]. Hence, miR-155, as a promoter of inflammatory responses, plays an important role by regulating the activation of immunocytes and the release of inflammatory cytokines. However, miR-155 can also control the intensity of the inflammatory response to microbial stimuli by targeting the Toll-like receptor/interleukin-1 (TLR/IL-1) inflammatory pathway in human dendritic cells (DCs) [20].

Recently, numerous studies have demonstrated that miR-155 is associated with hematological malignancies [25]. Transgenic miR-155 mice have also been shown to induce B cell malignancies *in vivo* [26]. With the exception of hematological malignancies, miR-155 can be detected in high levels in several solid tumors, such as CRC [12,13], lung cancer [13], breast cancer [13,27], thyroid carcinoma [28], cervical cancer [29], and pancreatic cancer [30,31], and it also serves as an indicator of a poor prognosis for patients with these tumors [32,33]. Several reports show that high levels of miR-155 are related to cancer cell invasion and poor survival [34,35]. At least 15%–20% of all human cancers are associated with chronic inflammation and diseases such as IBD (CRC and colitis-associated cancer), chronic gastritis, and *H. pylori* (gastric cancer, GC) [36]. miR-155, as a common target of a broad range of inflammatory mediators, may offer new insight into the mechanism of carcinoma. Hence, it is necessary to discuss the function of miR-155, which may act as a potential link between inflammation and cancer in the gastrointestinal tract.

3. *H. pylori*-Related Gastric Disease

H. pylori is a gram-negative spiral bacterium that was first described by Marshall and Warren in 1983 [37]. *H. pylori* acts as a primary pathogen because its presence in the stomach is almost always associated with a strong mucosal and systemic immune response [38]. *H. pylori* infection is often implicated in chronic gastritis, duodenal ulcer, gastric metaplasia, gastric extranodal marginal zone (MALT) lymphoma, and GC [39]. During *H. pylori* infection, miR-155 exhibits high expression levels in various cell types, including human T-cells, primary macrophages, and various epithelial cell lines, as well as in the gastric mucosa of infected mice and humans [11,15,40]. Similarly, miR-155 is up-regulated in *H. pylori*-positive gastritis [15], gastroduodenal ulcers [41,42], and

MALT lymphoma [43,44]. In conclusion, *H. pylori* infection may be relevant to the induction of miR-155 expression.

During *H. pylori* infection, the gastric epithelial cells recognize the TLRs of the bacteria and then may activate a series of inflammation-related signaling pathways. *H. pylori* LPS, a cell wall component, is recognized mainly by TLR4 [45]. TLR4 can activate the myeloid differentiation primary-response gene 88 (MyD88), leading to translocation of NF- κ B into the nucleus, subsequently activating the expression of genes related to the inflammatory process. Similarly, several TLR ligands have been shown to increase miR-155 expression via MyD88 [9]. Furthermore, up-regulation of miR-155 has been found to be dependent on the major *H. pylori* pathogenicity determinants, vacuolating toxin A (VacA), γ -glutamyl transpeptidase (GGT), and the type IV secretion system (T4SS) [40,46]. Related studies have indicated that *H. pylori* could induce miR-155 expression, which was dependent on the NF- κ B and activator protein-1 (AP-1) pathway but was independent of CagA [9,11]. In addition, *H. pylori* can also induce miR-155 in T-cells in a cAMP-Foxp3-dependent manner [40]. However, Kong *et al.* [47] showed that TGF- β can induce miR-155 expression and promoter activity through Smad4. Thus, the regulation of miR-155 is a complex process that may involve co-regulation of multiple factors and signaling pathways (Figure 1).

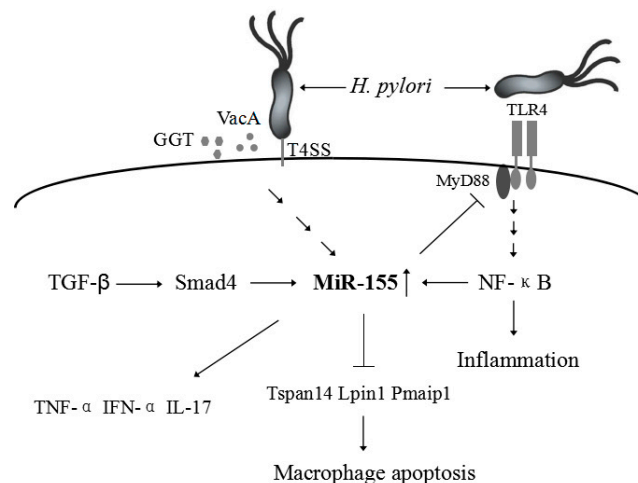


Figure 1. Overview of regulation of miR-155 by *H. pylori* infection.

Previous research has shown that *H. pylori* infections can be controlled by MHC class II-restricted Th1- and Th17-polarized Th cells in experimental murine models [48]. miR-155 has been shown to play a key role in T-cell-mediated control of *H. pylori* infections [15]. miR-155^{-/-} mice fail to control *H. pylori* infection as a result of impaired pathogen-specific Th1 and Th17 responses and exhibit significantly lower levels of gastric IFN- α and IL-17 production [15]. Similarly, overexpression of miR-155 by transfection of miR-155 mimics can significantly decrease the survival of intracellular *H. Pylori* [49]. Up-regulation of miR-155 can also lead to the expression of TNF- α [50]. miR-155 exhibits anti-apoptotic effects by targeting proapoptotic Tspan14, Lpin1, and Pmaip1, which could enhance the macrophage resistance to apoptosis induced by DNA damage during *H. pylori* infections [46]. Therefore, miR-155 is required for clearance of *H. pylori*. However, Xiao *et al.* [11] also noted that miR-155 may function as a negative regulator for the release of proinflammatory cytokines and signal transduction, which help to fine-tune the inflammatory response to *H. pylori* infection.

H. pylori infection is an important pathogenic factor in peptic ulcers; approximately 15%–20% of patients with a *H. pylori* infection develop peptic ulcer disease. However, all patients with a gastroduodenal ulcer are infected by *H. pylori* [51]. miR-155 is up-regulated during the development of *H. pylori*-infected gastroduodenal ulcers [41,42]. Cheng *et al.* [41] demonstrated that up-regulation of miR-155 and miR-146b decreased the over-expression of IL-6, impairing the immune response to

H. pylori (cagA+) and contributing to the development of *H. pylori* (cagA+)-infected gastroduodenal ulcers. miR-155 may play a role in immune inhibition during gastroduodenal ulcer development, leading to chronic gastroduodenal inflammation and subsequent ulcer development.

Gastric MALT lymphomas are often associated with chronic inflammation caused by a *H. pylori* infection. Saito *et al.* [43] found that the expression levels of miR-155 in gastric MALT lymphoma lesions were significantly higher than those in the corresponding non-tumor gastric mucosae using miRNA microarray analysis and quantitative RT-PCR; this is associated with *H. pylori* eradication by targeting tumor protein p53-inducible nuclear protein 1 (TP53INP), which induces cell cycle arrest and apoptosis. Therefore, the regulation and function of miR-155 in MALT lymphomas should continue to be evaluated.

GC is regarded as one of the most prevalent gastrointestinal cancers and has a low survival and high mortality rate. Development of gastric carcinoma involves multiple genetic lesions, such as oncogenes, tumor suppressor genes, and DNA mismatch repair genes [52,53]. Recently, many studies have demonstrated that miRNAs are closely correlated with GC development [54–57]. miRNAs have different expression levels in GC tissues that perform different functions. The expression levels of miR-155 in gastric carcinomas were significantly lower than those in the corresponding non-tumor gastric tissues [58]. Down-regulation of miR-155 accelerates cell growth and invasion by targeting c-myc in human gastric carcinoma cells [59]. c-myc serves as a pro-oncogene that is closely related to tumorigenesis and sustained tumor growth [60]. Thus, miR-155 may function as a gastric tumor suppressor during gastric carcinoma development. Similarly, Saito *et al.* [61] reported that up-regulation of miR-155 may inhibit GC cell metastasis by targeting Smad2. Thus, the regulation of miR-155 during gastric tumorigenesis is a complicated and poorly understood process.

Interestingly, during *H. pylori* infection, miR-155 exhibits increased expression in gastric mucosal tissues [11]; additionally, miR-155 is highly expressed during *H. pylori* positive gastritis [15], gastroduodenal ulcers [41,42], and MALT lymphoma [43,44]; however, miR-155 expression is reduced in GC cells and tissues [58,59]. miR-155 may play different roles in these diseases, and the process of gastric tumorigenesis is complex and may occur via silencing or loss of miR-155. Heterogeneity in biological functions could be another reason for these differences. Up-regulated miR-155 induced by *H. pylori* infections may contribute to the inflammatory response in *H. pylori*-related gastric disease.

4. Intestinal Diseases

The intestinal mucosal barrier plays an indispensable role in maintaining normal intestinal function and is composed of a layer of cross-linked, highly differentiated epithelial cells located at the apical junction complex (AJC). miR-155 over-expression inhibits RhoA protein expression, which down-regulates the expression of zonula occludens-1 (ZO-1) and E-cadherin, two major component proteins of the AJC [62]. Many inflammatory cytokines, such as TNF- α and interferons, also reduce the mucosal barrier function by destroying the AJC [63,64]. Similarly, miR-155 expression can be induced by TNF- α and interferons [9,50,65,66]. Thus, the regulation of miR-155 plays a key role in intestinal mucosal barrier function, which is closely associated with intestinal diseases.

IBD refers to chronic inflammatory disorders of the gut with unclear pathogenesis, including Crohn's disease (CD) and ulcerative colitis (UC) [67]. IBD is characterized by underlying immunological deregulation, a susceptible genetic background, and intestinal microbes that lead to damage of the intestinal mucosa [68,69]. In IBD, mucosal inflammation may be caused by an intestinal barrier injury, which may result from increasing permeability and destruction of the tight junctions [70].

Deregulated miRNA expression is involved in a variety of disorders, such as IBD [71,72]. Several studies have shown that the expression of miR-155 is increased in IBDs including UC and CD [73–75]. When miRNA expression profiles were analyzed in patients with active UC, miR-155 was up-regulated in patients with active UC compared to healthy subjects, resulting in a direct down-regulation of the expression of Forkhead box O3 (FOXO3a), which may activate the NF- κ B signaling pathway

and up-regulate inflammatory cytokines such as IL-8 [76,77]. The pathogenic mechanism of UC, which may involve multiple immune process and immunological inflammation, is currently unclear. The inflammatory process of the intestinal mucosa involves many intestinal stromal cells such as mesenchymal cells, including intestinal fibroblasts and myofibroblasts (IMFs) [78]. In UC, miR-155 modulates the inflammatory phenotype of IMFs by targeting the suppressor of cytokine signaling 1 (SOCS1), which is a known feedback inhibitor of inflammation [79]. Thus, this is an effective approach that results in decreasing deregulated cytokine release from IMFs by suppressing miR-155. Previous studies have indicated that T-cell-mediated injury may be a pathogenic pathway for the intestinal damage associated with IBD [80]. Loss of miR-155 protects mice from experimental colitis, which involves multiple pathways, including decreased TNF- α , IL-6, IL-12, IL-17, and IFN- γ production, decreased Th1 responses and reduced activation of T-cells by DCs [81]. Inhibition of the target of miR-155 can diminish the release of inflammatory cytokines and reduce the severity of colitis. This finding shows that miR-155 inhibition may be a novel and effective therapeutic target for colitis and IBD.

CRC was the third most commonly-diagnosed cancer in males and the second most commonly diagnosed cancer in females in 2012, and its incidence is increasing in several Asian and Eastern European countries [82]. Although the development of CRC therapy is proceeding at a fast pace, the prognosis of advanced CRC is still very poor. Thus, clarifying the pathogenesis of CRC is highly desirable. A relationship between miRNA function and cancer pathogenesis has been demonstrated. In real-time PCR analysis, many miRNAs exhibit different expression levels in CRC and non-tumoral tissues [83,84]. Similarly, over-expression of miR-155 has been detected in CRC [12,13]. Qu *et al.* [12] noted that miR-155 could promote proliferation, invasion, and metastasis of CRC cells; its up-regulation was closely related to tumor location, tumor grade, Tumor Node Metastasis (TNM) staging, and distant metastasis in CRC. In general, the mismatch repair (MMR) system is widely present in many organisms, acts as the repair mechanism after cell replication, and maintains the fidelity of DNA replication. miR-155 causes a decrease in MMR protein stability and down-regulates core MMR proteins in the MMR system in CRC, thus inducing microsatellite instability (MSI) [85]. MSI is divided into three types: high levels of MSI (MSI-H), low levels of MSI (MSI-L) and microsatellite stability (MSS). In CRC, increased relative expression of miR-155 is more significantly associated with MSI-H status than with MSI-L and MSS status [86]. Similarly, miR-155 overexpression is particularly associated with MSI in IBD and CRCs and extends to the distant non-neoplastic mucosa [87]. In summary, miR-155 over-expression may induce MSI by regulating the MMR system, thus promoting MSI-driven neoplastic transformation of the colonic mucosa. However, miR-155 over-expression may play a role in oncogenesis by combining with inflammatory stimuli in tumor cells. These changes may indicate the potential pathogenetic mechanism of CRC. Further research is needed to identify an intervention for this mechanism.

5. Discussion and Conclusions

miR-155 can regulate innate and adaptive immunity, which control antibody production and cytokine release. Although regulation of miR-155 has been widely studied in the innate immune process and immune-mediated diseases, it has also recently become the focus of study for various malignancies. In this review, we report the expression and function of miR-155 in gastrointestinal diseases such as *H. pylori*-related gastric disease, IBD, and CRC (Table 1). miR-155 may be a suitable choice for use as an interesting and innovative therapeutic target or a biomarker of disease type and severity for certain human cancers. However, a recent study found that increased miR-155 expression was correlated with an improved prognosis in human melanoma patients [88]. This condition may explain the dysregulation of miR-155, which may be a direct negative regulator of GC cell proliferation and survival in GC patients. However, the exact carcinogenic mechanism of miR-155 is not entirely clear; therefore, more studies that lead to an understanding of the role and pathogenic mechanisms of miR-155 are necessary to search for effective treatment modalities for these gastrointestinal diseases.

miR-155 may be an attractive candidate for the development of new therapeutic interventions in the near future.

Table 1. Role of miR-155 in diseases of the gastrointestinal tract.

Disease	Expression	Function	Target(s)
<i>H. pylori</i>-related gastric disease			
<i>H. pylori</i> infection	Up-regulation	Decreases the survival of intracellular <i>H. Pylori</i> [49], induces the expression of TNF- α [50], enhances the macrophage resistance to apoptosis [46], or reduces the release of proinflammatory cytokines and signal transduction [11].	Tspan14, Lpin1, and Pmaip1 [46]
Peptic ulcers	Up-regulation	Decreases the over-expression of IL-6 and impairs the immune response to <i>H. pylori</i> (cagA+) [41].	
Gastric MALT lymphomas	Up-regulation	Induces cell cycle arrest and apoptosis [43].	TP53INP [43]
GC	Down-regulation	Accelerates cell growth and invasion in human gastric carcinoma cells [59], inhibit GC cell metastasis [61].	c-myc [59], Smad2 [61]
Intestinal diseases			
IBD	Up-regulation	Activates the NF- κ B signaling pathway and up-regulate inflammatory cytokines such as IL-8 [76], modulates the inflammatory phenotype of IMFs [79], Loss of miR-155 protects mice from experimental colitis by decreasing TNF-(IL-6, IL-12, IL-17, and IFN- γ production [81].	FOXO3a [76], SOCS1 [79]
CRC	Up-regulation	Promotes proliferation, invasion, and metastasis of CRC cells, is closely related to tumor location, tumor grade, TNM staging, and distant metastasis in CRC [12], induces MSI by regulating the MMR system [85].	

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Abbreviations

AJC	apical junction complex
CRC	colorectal cancer
CD	Crohn’s disease
GC	gastric cancer
GGT	γ -glutamyl transpeptidase
IBD	inflammatory bowel disease
IMFs	intestinal fibroblasts and myofibroblasts
MMR	mismatch repair
MSI	microsatellite instability
MyD88	myeloid differentiation primary-response gene 88
poly IC	polyriboinosinic-polyribocytidylic acid
RISC	RNA-induced silencing complex
SOCS1	suppressor of cytokine signaling 1
T4SS	type IV secretion system
TLR/IL-1	Toll-like receptor/interleukin-1
TP53INP	tumor protein p53-inducible nuclear protein 1
UC	ulcerative colitis
VacA	vacuolating toxin A

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