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The role of microRNAs in the development of gastric and duodenal ulcers

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Abstract

The research highlights the fundamental concepts of microRNA, the mechanisms of RNA interference, the importance of microRNA in the development of diseases. Combining the experience of domestic and foreign researchers, the authors identified the main miRNAs involved in the development of gastric and duodenal ulcers. The article also describes the main mechanisms of regulation of the inflammatory process in gastric and duodenal ulcers associated with *Helicobacter pylori*, the influence of microorganisms on the expression of various microRNA types and the control of the cellular immune response. In addition, the review presents the latest research on methods for diagnosing *Helicobacter pylori*-associated peptic ulcer based on the determination of circulating microRNAs. The results of an experimental model of treatment of patients infected with *Helicobacter pylori* with drugs that act on non-coding RNA are presented.

Keywords: microRNA, peptic ulcer, morbidity, complicated gastric and duodenal ulcer, review.

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Deoxyribonucleic acid (DNA) stores and transfers genetic information across generations, whereas ribonucleic acid (RNA) codes, reads, regulates, and expresses genes [1].

Before 1993, RNAs in cells were considered to exist in three primary forms: matrix (informational) RNA, transport RNA, and ribosomal RNA [2]. However, in 1993, A. Ambros, R. Lee, and R. Feinbaum in 1993, examining the role of *lin-14* gene in the development of the nematode *Caenorhabditis elegans*, revealed that the amount of protein encoded by *lin-14* is regulated by short (micro) RNAs [3]. Subsequent studies have shown that numerous small noncoding RNAs, known as microRNAs, are responsible for the development of various diseases [4–10]. MicroRNAs typically range from 18 to 25 nucleotides in length, and >2000 have been detected in humans [11].

Up to 60% of protein-coding genes are targeted by microRNAs, which block gene expression through RNA interference [13–15]. This provides protection against viruses and foreign genetic materials. MicroRNAs can regulate hundreds of genes, and a single gene can be regulated by hundreds of microRNAs. Kiseleva et al. (2019) demonstrated the ability of microRNAs to transfer between cells via vesicles [19].

The immune system and an organism's reparative capabilities depend on the participation of microRNAs in gene expression [20–22]. Noncoding microRNAs are involved in all processes of human body activity, including disease development [23]. Recent studies have suggested that microRNAs can be used as biomarkers of pathological conditions in the future [24, 25]. Genetic research can predict the presence, course, stage, and outcome of diseases [26–28]. Russian and foreign scientists have emphasized the importance of studying the relationship between microRNAs and diseases.

S. Lario et al. [29] conducted one of the first studies on microRNAs in gastric and duodenal ulcer diseases. This study compared microRNA expression between patients with peptic ulcer disease and *Helicobacter pylori* infection and those suffering from the disease but without *H. pylori* infection. The study found that the expression of microRNA-9, microRNA-96, microRNA-146a, microRNA-155, and microRNA-650 was specific to chronic active gastritis.

A study also found that chronic active gastritis was associated with a significant increase in the expression levels of microRNA-650 (10-fold), microRNA-146a (6-fold), and microRNA-155 (3-fold).

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In the gastric antral region, patients with *H. pylori* infection exhibited higher expression levels of microRNA-9, microRNA-146a, microRNA-155, and microRNA-650. However, no direct correlation was found between microRNAs and peptic ulcer disease. Thus, the relationship between *H. pylori* and microRNA activation is still unclear [30].

S. Lario et al. reported that microRNA-146 and microRNA-223 families, along with microRNA-155-5p, play a crucial role in regulating inflammation [31].

Similarly, S.F. Cheng et al. revealed that microRNA-155 and microRNA-146b are active in patients with gastroduodenal ulcers and *H. pylori* infection. Infection induced increased expression levels of IL-6 and AGS proteins through exposure to the two aforementioned microRNAs at different time points [32]. In addition, the expression level of microRNA-146a was significantly upregulated (7-fold) in gastric epithelial cells of patients with *H. pylori* infection [33]. Other studies have also reported abnormal expression of microRNA-155 in patients with *H. pylori* infection [34, 35].

In peptic ulcer disease, the expression of this microRNA is abnormally high, which increased 3.9-fold. However, in patients with inflammatory bowel disease and colorectal cancer, the expression rate is only slightly increased by 1.2-fold [36, 37].

The pathogenesis of *H. pylori* infection and the activation of various microRNA types have been studied extensively, creating several theories on their regulation. In 2018, Na Li et al. discovered that microRNA-146a overexpression regulates inflammatory responses by inhibiting tumor necrosis factor and interleukin (IL)-1 genes. They also revealed that *H. pylori* infection stimulates IL-17A synthesis, which leads to increased production of microRNA-146a in gastric epithelial cells. In addition, microRNA-146a overexpression in SGC-7901 cells suppressed IL-17A-induced inflammatory responses. The expression levels of IRAK1 and TRAF6, which have been implicated in IL-17A-mediated inflammation, was also suppressed. These findings suggest that microRNA-146a induced by IL-17A may be a negative regulator of the inflammatory response in the gastric mucosa during *H. pylori* infection [38].

MicroRNAs play a role in the immunity of patients with *H. pylori* infection. They regulate the maturation, proliferation, differentiation, and activation of immune cells and participate in the regulation of immune responses [39].

Wang et al. [40] demonstrated the regulation of inflammatory processes in the gastric mucosa by correcting cellular immunity. They revealed that microRNA-223 can suppress the immune response

against *H. pylori*. Macrophages, which are the first line of host immune cells to counter *H. pylori* infection in gastric tissues [41], have enhanced immune responses against *H. pylori* because of the presence of microRNAs. This helps to avoid excessive damage.

MicroRNA-223 was found to inhibit the expression of inflammatory cytokines, such as IL-6, IL-8, and IL-12, and tumor necrosis factor- α . It can also reduce the expression levels of CD40, CD68, CD80, and CD163 [42]. Furthermore, *H. pylori* suppresses the inflammatory response and reduces immune attack by activating the expression of various microRNAs [43].

The transition from a proinflammatory response to an anti-inflammatory one enables the pathogens to spread to the mucous membrane of the upper gastrointestinal tract sustainably and survive for an extended period. Pachathundikandi et al. described this mechanism of immune response regulation, demonstrating that microRNA-223-3p was induced by bacteria and controlled the inflammatory process [44].

Mohamed et al. examined the effect of microRNAs on the progression of *H. pylori*-associated peptic ulcer to gastric cancer and discovered significantly higher expression levels of microRNA-204 and microRNA-182 (12.5-fold and 2.6-fold, respectively) in patients with peptic ulcer disease than in healthy individuals. They also found that the higher expression levels of the aforementioned microRNAs were associated with increased expression levels of inflammatory factors such as tumor necrosis factor- α , IL-1, and IL-6 [45]. The potential of studying microRNA-34a expression levels in peptic ulcer disease, dysplasia, and gastric cancer is promising because microRNA genes are regulated by p53 [46]. The activation of the microRNA-34 family results in apoptosis, cell cycle arrest, and cellular aging [47].

A.A. Arkhipova found an inverse correlation between microRNA let-7b and IL-1B levels, microRNA-103 and IL-6 levels, microRNA-375 and IL-8 levels, and microRNA-200a and tumor necrosis factor- α [48]. Changes in the level of microRNA-204, which regulates the expression of matrix metalloproteinase 9, have been observed in ulcer formation, peptic ulcer recurrence, and gastric cancer. During infection of the gastric mucosa with *H. pylori*, some microRNAs exhibit altered indicators and are associated with ulcer disease, Correa cascade, and development of MALT lymphoma.

Levels of microRNA-150, microRNA-550, microRNA-124a, microRNA-518b, and microRNA-539 change in response to lymphocyte infiltration in the presence of *Helicobacter* infection. In addition,

microRNA-21 overexpression has been observed in *H. pylori* infection of the gastric mucosa [49].

As previously stated, a single microRNA can affect multiple protein-coding genes, resulting in various conditions. Li and Wang [50] used the Gene Expression Omnibus database and MiRnet software to present a comparative analysis of two dataset groups: GSE54710 and GSE32174. They analyzed microRNA expression data for periodontitis and *Helicobacter*-associated duodenal ulcers. The results showed that both conditions share common upregulated microRNAs, genes, and transcription factors, including microRNA-155-5p, microRNA-484, microRNA-29a-3p, PTEN, CCND1, MDM2, TNFR-C6A, STAT3, HIF1A, EZH2, CEBPA, and RUNX1.

Circulating microRNAs have demonstrated significant potential as noninvasive biomarkers for diagnosing infectious diseases [51]. Yu et al. analyzed the expression levels of blood plasma microRNAs as noninvasive biomarkers of *H. pylori* infection. After analyzing microRNA expression in the plasma of 63 patients with *H. pylori* infection and 41 healthy volunteers, the researchers discovered that 37 microRNAs were activated in patients with *H. pylori* infection compared with healthy volunteers. The expression levels of microRNA-28-3p, microRNA-143-3p, microRNA-151a-3p, and microRNA-148a-3p are closely associated with *H. pylori* infection [52].

While some researchers are investigating the mechanisms of disease development and developing diagnostic methods based on microRNA expression analysis, others are developing treatment methods that rely on the effect of drugs on noncoding RNAs. For instance, Xin-yi et al. replicated an experiment by uploading the required data to cloud storage and established a connection between key genes, microRNAs, and a new herbal drug containing Baikal hellebore roots and coptis rhizome. The investigated drug can regulate microRNA-93-5p, microRNA-374b-5p, and microRNA-3937, resulting in a positive therapeutic effect [53].

The analysis of modern literature suggests that numerous microRNAs may contribute to the pathogenesis of peptic ulcer disease. Clarifying their role in disease development is a pressing issue in modern medicine and offers the potential for a new treatment direction for patients with peptic ulcer disease.

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