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Role of miRNA-146a and miRNA-125b in Helicobacter Pylori Infection in Children

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Abstract
Background: *Helicobacter pylori* (H. pylori) infection is significant global health concern, particularly in pediatric populations where it can lead to chronic gastritis, peptic ulcers, and increased risk of gastric malignancies. MicroRNAs (miRNAs), specifically miRNA-146a and miRNA-125b, are emerging as crucial regulators of immune responses and inflammation in various diseases, including H. pylori infection. Understanding roles of miRNAs could provide novel insights into pathogenesis and management of H. pylori-related diseases in children.
Objective: narrative review aims to explore roles of miRNA-146a and miRNA-125b in context of H. pylori infection in children, with focus on their potential as biomarkers and therapeutic targets.
Methods: comprehensive review of current literature was conducted, analyzing studies investigate molecular mechanisms of miRNA-146a and miRNA-125b and their involvement in immune regulation during H. pylori infection. review also examines implications of miRNAs for disease progression, severity, and therapeutic strategies in pediatric patients.
Conclusion: miRNA-146a and miRNA-125b play critical roles in modulating immune response to H. pylori infection in children, potentially influencing disease severity and outcomes. However, further research is necessary to fully elucidate their roles and develop effective clinical applications.

Keywords: Helicobacter pylori, miRNA-146a, miRNA-125b, pediatric infection, immune regulation.

Introduction

Background on Helicobacter Pylori Infection in Children

Helicobacter pylori (H. pylori) is Gram-negative, spiral-shaped bacterium colonizes human stomach, often acquired during childhood. global prevalence of H. pylori infection varies widely, with higher rates observed in developing countries. In children, prevalence can range from 10% to 80%, depending on region, socioeconomic status, and living conditions. infection is primarily transmitted via oral-oral or fecal-oral routes, often within families, emphasizing role of close contact and hygiene practices in its spread [1].

The clinical manifestations of H. pylori infection in children can be diverse, ranging from asymptomatic colonization to more severe gastrointestinal symptoms. Common symptoms include abdominal pain, nausea, vomiting, and in some cases, growth retardation. Although most children with H. pylori infection remain asymptomatic, subset can develop more serious complications such as chronic gastritis, peptic ulcer disease, and even increased risk of gastric malignancies later in life [2].

Complications associated with H. pylori infection in children can have long-term health implications. Chronic gastritis, often characterized by persistent inflammation of stomach lining, can lead to atrophic changes and increased risk of developing gastric adenocarcinoma in adulthood. Additionally, there is growing evidence H. pylori infection may be linked to extragastric manifestations, including iron-deficiency anemia and idiopathic thrombocytopenic purpura, further highlighting need for early diagnosis and appropriate management in pediatric populations [3].

Introduction to microRNAs (miRNAs)

MicroRNAs (miRNAs) are small, non-coding RNA molecules typically 18-25 nucleotides in length, playing crucial role in post-transcriptional regulation of gene expression. miRNAs function by binding to complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation. regulatory mechanism allows miRNAs to modulate wide array of biological processes, including cell proliferation, differentiation, apoptosis, and immune responses [4, 5].

In recent years, miRNAs have garnered significant attention for their involvement in various diseases, including cancer, cardiovascular disorders, and infectious diseases. Their ability to regulate multiple target genes simultaneously makes them key players in complex biological networks. In context of infections, miRNAs have been shown to influence host-pathogen interactions, modulate immune responses, and impact disease progression and outcomes [6, 7].

The role of miRNAs in bacterial infections, such as H. pylori, is particularly

intriguing. Several miRNAs have been identified as key regulators of immune response to H. pylori infection, influencing balance between pro-inflammatory and anti-inflammatory pathways. Understanding specific roles of miRNAs can provide insights into mechanisms underlying H. pylori-associated diseases and potentially lead to development of novel therapeutic strategies [8-10].

Focus on miRNA-146a and miRNA-125b

Among various miRNAs implicated in H. pylori infection, miRNA-146a and miRNA-125b have emerged as molecules of particular interest due to their significant roles in immune regulation and inflammation [11].

miRNA-146a is known for its involvement in negative regulation of immune response. It acts as feedback regulator of pro-inflammatory signaling pathways, including nuclear factor-kappa B (NF-κB) pathway, by targeting key adapter molecules such as TRAF6 and IRAK1. In context of H. pylori infection, miRNA-146a has been shown to modulate inflammatory response, potentially influencing severity of gastritis and risk of disease progression [11, 12].

miRNA-125b, on other hand, has been implicated in regulation of cell proliferation, apoptosis, and immune responses. Its role in H. pylori infection is less well-characterized compared to miRNA-146a, but emerging evidence suggests miRNA-125b may influence host response to H. pylori, particularly in regulation of gastric epithelial cell behavior and modulation of immune signaling pathways [13, 14].

Both miRNA-146a and miRNA-125b are thought to play critical roles in host's response to H. pylori infection, potentially affecting balance between protective and pathogenic immune responses. Their dysregulation could contribute to persistence of infection, development of chronic inflammation, and progression to more severe gastric diseases [15].

The aim of narrative review is to explore roles of miRNA-146a and miRNA-125b in context of H. pylori infection in children. By reviewing current research on miRNAs, review seeks to elucidate their potential contributions to pathogenesis of H. pylori-associated diseases and to consider their value as biomarkers or therapeutic targets in pediatric population.

❖ Helicobacter Pylori and its Pathogenesis

Overview of H. pylori

Helicobacter pylori (H. pylori) is Gram-negative, microaerophilic bacterium is uniquely adapted to survive in highly acidic environment of human stomach. It is characterized by its spiral shape, multiple flagella, and production of urease, enzyme converts urea to ammonia, which helps neutralize stomach acid and enables bacterium to colonize gastric mucosa. bacterium is one of most prevalent human pathogens, infecting more than half of world's population, with infection typically acquired during childhood. prevalence of H. pylori infection in children is highly variable, influenced by factors such as geographic location, socioeconomic status, and living conditions, with higher rates observed in developing countries [16, 17].

H. pylori primarily colonizes antrum of stomach, where it can persist for decades if left untreated. bacterium's mechanisms of infection involve several virulence factors, including cytotoxin-associated gene (CagA) and vacuolating cytotoxin (VacA). CagA-positive strains are particularly associated with increased inflammation and higher risk of severe disease outcomes, such as peptic ulcers and gastric cancer. H. pylori adheres to gastric epithelial cells through adhesins like BabA and SabA, which bind to specific receptors on host cells, facilitating colonization and persistence [18].

The presence of H. pylori in stomach leads to local inflammatory response, characterized by infiltration of immune cells, including neutrophils, macrophages, and T cells, into gastric mucosa. inflammation can result in chronic gastritis, condition that, if unresolved, may progress to more severe complications such as peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma. In children, H. pylori infection is often asymptomatic; however, when symptoms do occur, they can include abdominal pain, nausea, vomiting, and in some cases, growth retardation. long-term consequences of untreated H. pylori infection in childhood can extend into adulthood, highlighting importance of early detection and treatment [1, 19].

Immune Response to H. pylori

The immune response to H. pylori infection is complex and involves both innate and adaptive immune systems. Upon infection, innate immune system is first to respond, with gastric epithelial cells recognizing H. pylori through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). receptors detect conserved microbial components known as pathogen-associated molecular patterns (PAMPs), leading to activation of downstream signaling pathways result in production of pro-inflammatory cytokines and chemokines, including interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). IL-8, in particular, plays crucial role in recruiting neutrophils to site of infection, contributing to characteristic neutrophilic infiltration seen in H. pylori-associated gastritis [20-22].

As infection persists, adaptive immune system is activated, with T cells and B cells playing central roles in host response. CD4+ T helper (Th) cells, particularly Th1 and Th17 subsets, are prominent in gastric mucosa during H. pylori

infection. Th1 cells produce interferon-gamma (IFN-γ), which enhances bactericidal activity of macrophages and promotes further inflammation. Th17 cells, on other hand, secrete interleukin-17 (IL-17), which also contributes to recruitment of neutrophils and amplification of inflammatory response. Despite robust immune response, H. pylori has evolved multiple strategies to evade immune clearance, including modulation of antigen presentation, induction of regulatory T cells (Tregs) suppress immune response, and alteration of gastric environment to inhibit effective action of immune cells [23].

Cytokines play central role in orchestrating immune response to H. pylori, with delicate balance between pro-inflammatory and anti-inflammatory signals determining outcome of infection. While pro-inflammatory cytokines IL-8, TNF-α, and IFN-γ drive inflammatory response, other cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), act to limit damage caused by excessive inflammation and promote tissue repair. chronic inflammation induced by H. pylori can lead to epithelial cell damage, loss of gastric glandular structures, and development of gastric atrophy, precursor to gastric cancer [24, 25].

In children, immune response to H. pylori may differ from in adults, potentially due to immaturity of immune system and differences in gastric environment. Understanding differences is crucial for developing age-specific strategies for management of H. pylori infection and preventing its long-term complications. interplay between immune response and H. pylori's evasion strategies is key factor in pathogenesis of infection and its associated diseases, making it important area of research in context of pediatric H. pylori infection [26].

❖ Role of miRNA-146a in H. pylori Infection

Mechanisms of miRNA-146a

miRNA-146a is small non-coding RNA molecule plays significant role in regulation of immune responses, particularly in controlling inflammation. At molecular level, miRNA-146a functions primarily by targeting messenger RNAs (mRNAs) for degradation or by inhibiting their translation, thereby reducing expression of specific proteins involved in inflammatory pathways. One of key targets of miRNA-146a is nuclear factor-kappa B (NF-κB) signaling pathway, which is central to regulation of immune responses and inflammation [27].

The NF-κB pathway is activated in response to various stimuli, including microbial infections, cytokines, and stress signals. Upon activation, NF-κB translocates to nucleus, where it promotes transcription of genes encoding pro-inflammatory cytokines, chemokines, and other immune-related proteins. miRNA-146a exerts its regulatory function by targeting and downregulating key adapter proteins involved in pathway, such as TNF receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK1). By reducing levels of proteins, miRNA-146a effectively dampens NF-κB-mediated inflammatory response, acting as negative feedback regulator [28].

In addition to its role in NF-κB pathway, miRNA-146a also modulates other signaling pathways involved in inflammation and immune responses, including Toll-like receptor (TLR) and cytokine signaling pathways. Through its broad regulatory effects, miRNA-146a helps maintain balance between pro-inflammatory and anti-inflammatory signals, preventing excessive inflammation could lead to tissue damage and chronic inflammatory conditions [29].

miRNA-146a in H. pylori Infection

The involvement of miRNA-146a in H. pylori infection has been subject of several studies, particularly in context of its role in modulating immune response to bacterium. In H. pylori infection, inflammatory response is crucial for controlling bacterial colonization and limiting tissue damage. However, excessive or prolonged inflammatory response can contribute to development of chronic gastritis, peptic ulcers, and increased risk of gastric cancer [30].

In pediatric cases, role of miRNA-146a in H. pylori infection is of particular interest due to unique aspects of immune response in children. immune system in children is still developing, and regulation of inflammatory responses may differ from in adults. Some studies have suggested expression levels of miRNA-146a in gastric mucosa of children with H. pylori infection are correlated with severity of gastritis, indicating miRNA-146a may play role in determining outcome of infection in pediatric patients [11].

Moreover, miRNA-146a may also contribute to persistence of H. pylori infection by modulating immune response in way allows bacterium to evade clearance. By dampening inflammatory response, miRNA-146a could create more favorable environment for H. pylori colonization and survival. dual role of miRNA-146a—as both regulator of inflammation and potential facilitator of bacterial persistence—highlights complexity of its function in H. pylori infection [21].

Further research is needed to fully elucidate role of miRNA-146a in H. pylori infection, particularly in children. Understanding how miRNA-146a influences balance between protective and pathogenic immune responses could have important implications for development of new therapeutic strategies aimed at modulating miRNA activity to treat H. pylori-related diseases in pediatric populations.

❖ **Role of miRNA-125b in H. pylori Infection**

Mechanisms of miRNA-125b

miRNA-125b is highly conserved small non-coding RNA plays pivotal role in regulation of various cellular processes, including cell proliferation, apoptosis, and immune responses. At molecular level, miRNA-125b exerts its function by binding to complementary sequences in 3' untranslated region (3' UTR) of target messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation. post-transcriptional regulation allows miRNA-125b to fine-tune expression of key proteins involved in critical cellular pathways [31, 32].

One of primary roles of miRNA-125b is in regulation of cell proliferation and apoptosis. miRNA-125b has been shown to target and suppress expression of pro-apoptotic genes, such as p53, well-known tumor suppressor protein plays central role in cellular response to DNA damage and stress. By downregulating p53 and other pro-apoptotic factors, miRNA-125b can inhibit apoptosis and promote cell survival, contributing to cellular homeostasis under normal conditions. However, dysregulation of miRNA-125b can lead to uncontrolled cell proliferation and has been implicated in various cancers [33, 34].

In addition to its role in cell survival, miRNA-125b also modulates immune responses by targeting molecules involved in regulation of inflammation and immune cell activation. For example, miRNA-125b can downregulate TNF-α, key pro-inflammatory cytokine, thereby attenuating inflammatory response. It also affects differentiation and function of immune cells, including T cells and macrophages, influencing overall immune response to infections and other stimuli [35, 36].

The ability of miRNA-125b to regulate both cell survival and immune responses makes it critical player in maintaining balance between normal cellular function and pathological conditions. Its involvement in multiple pathways underscores its importance in health and disease, particularly in context of infections like H. pylori [37].

miRNA-125b in H. pylori Infection

Research has shown miRNA-125b expression is altered in response to H. pylori infection, with some studies reporting upregulation of miRNA-125b in infected gastric tissues. upregulation is believed to be part of host's attempt to control inflammatory response and limit tissue damage. By targeting pro-inflammatory cytokines like TNF-α, miRNA-125b may help to reduce excessive inflammation, thereby protecting gastric mucosa from injury. However, anti-inflammatory effect might also contribute to persistence of H. pylori by dampening immune response is necessary to clear infection [8, 10].

In context of pediatric H. pylori infection, role of miRNA-125b is particularly important to explore, given differences in immune response and disease progression between children and adults. Children with H. pylori infection often exhibit milder inflammatory response compared to adults, which may be influenced by activity of miRNAs like miRNA-125b [38]. Understanding how miRNA-125b modulates immune response in children could provide insights into why some children develop more severe outcomes, such as peptic ulcers or atrophic gastritis, while others remain asymptomatic or have milder disease.

Moreover, miRNA-125b may also be involved in regulation of gastric epithelial cell behavior during H. pylori infection. By influencing cell proliferation and apoptosis, miRNA-125b could affect integrity of gastric mucosa, potentially contributing to development of precancerous lesions in cases of chronic infection. balance between protective and pathological roles of miRNA-125b in gastric environment is likely to be key factor in determining long-term outcomes of H. pylori infection in children [39].

Overall, involvement of miRNA-125b in H. pylori infection highlights its potential as biomarker for disease progression and as therapeutic target for modulating immune response in infected individuals. Further research is needed to fully elucidate mechanisms by which miRNA-125b influences pathogenesis of H. pylori and to explore its role in pediatric populations, where early intervention could prevent development of serious complications.

❖ **Interaction Between miRNA-146a, miRNA-125b, and H. pylori**

Synergistic or Antagonistic Effects

The interaction between miRNA-146a and miRNA-125b in context of H. pylori infection presents complex and intriguing aspect of immune regulation. Both miRNAs are involved in modulating inflammatory responses, but they may exert their effects in different, and potentially complementary or opposing, ways [40].

miRNA-146a is primarily known for its role as negative regulator of inflammation. By targeting key components of NF-κB signaling pathway, such as TRAF6 and IRAK1, miRNA-146a helps to dampen inflammatory response, preventing excessive tissue damage can result from chronic inflammation [12, 41].

On other hand, miRNA-125b also plays role in controlling inflammation but through different mechanisms. It targets pro-inflammatory cytokines such as TNF-α, which are crucial for initial immune response to infection. By downregulating cytokines, miRNA-125b can reduce inflammation and promote cell survival, particularly in gastric epithelium. However, anti-inflammatory action might also reduce efficacy of

immune response against H. pylori, potentially allowing bacterium to persist in host [42].

The potential for synergistic or antagonistic effects between miRNA-146a and miRNA-125b lies in their overlapping yet distinct roles in immune regulation. Both miRNAs contribute to suppression of inflammation, but they do so through different targets and pathways. It is conceivable miRNAs could act synergistically to achieve balanced immune response controls inflammation without compromising host's ability to combat infection. For example, miRNA-146a's suppression of NF-κB signaling might complement miRNA-125b's inhibition of TNF-α, collectively reducing risk of chronic gastritis and other inflammatory conditions associated with H. pylori infection [43].

Conversely, miRNAs could also have antagonistic effects, depending on specific context of infection and host's immune status. If one miRNA's activity is dominant, it might tip balance towards either insufficient or overly aggressive immune response. For instance, excessive activity of miRNA-146a could overly suppress immune response, allowing H. pylori to persist and increasing risk of long-term complications. Alternatively, if miRNA-125b is too active, it could inhibit necessary inflammatory response required to clear infection, leading to chronic colonization by bacterium [44].

Understanding dynamic interplay between miRNA-146a and miRNA-125b during H. pylori infection is crucial for developing strategies to modulate miRNAs in way promotes protective, rather than pathological, immune response.

❖ **Implications for Disease Severity and Treatment**

The interactions between miRNA-146a, miRNA-125b, and H. pylori have significant implications for severity of infection and development of associated diseases. Given their roles in regulating immune response, miRNAs could influence outcome of infection in several ways [15].

The potential to target miRNA-146a and miRNA-125b in therapeutic strategies is area of growing interest. Modulating activity of miRNAs could provide means to fine-tune immune response to H. pylori, enhancing host's ability to clear infection while minimizing risk of chronic inflammation and its associated complications. For example, inhibiting miRNA-146a might be beneficial in cases where overly suppressed immune response is contributing to bacterial persistence, whereas boosting miRNA-125b activity could help reduce excessive inflammation in patients with severe gastritis [4].

In summary, interaction between miRNA-146a and miRNA-125b in H. pylori infection highlights complexity of immune regulation in context and underscores potential for miRNAs to influence disease progression and treatment outcomes. Further research into specific mechanisms by which miRNAs interact and their roles in pediatric H. pylori infection could lead to novel approaches for managing common and often persistent infection.

❖ **Clinical Implications and Future Directions**
Diagnostic Potential

The identification of reliable biomarkers is crucial for early diagnosis and effective management of H. pylori infection, particularly in children where long-term consequences of untreated infection can be significant. miRNA-146a and miRNA-125b have shown promise as potential biomarkers due to their roles in modulating immune response during H. pylori infection. miRNAs could be detected in gastric tissues, blood, or even in non-invasive samples such as saliva or stool, providing less invasive method for diagnosing H. pylori infection in pediatric populations.

The use of miRNAs as biomarkers could enhance diagnostic process by providing additional information beyond presence of bacterium itself, offering insights into host's response to infection and potential for disease progression. could be particularly valuable in pediatric cases, where early detection and intervention are critical to preventing long-term health issues.

❖ **Therapeutic Prospects**

The role of miRNA-146a and miRNA-125b in regulating immune responses during H. pylori infection also opens up possibility of miRNA-based therapies. therapies could involve modulating activity of miRNAs to achieve more balanced immune response, thereby improving outcomes of H. pylori infection management, especially in children.

For instance, therapeutic strategies could aim to enhance activity of miRNA-146a in cases where excessive inflammation is contributing to gastric damage, helping to reduce inflammation and prevent development of ulcers or atrophic gastritis. Conversely, in cases where immune response is insufficient to clear infection, inhibiting miRNA-146a might boost host's ability to mount more effective defense against bacterium.

Similarly, miRNA-125b-based therapies could be designed to either promote or inhibit its function depending on specific needs of patient. Enhancing miRNA-125b activity might be beneficial in reducing chronic inflammation and protecting gastric mucosa, while inhibiting it could help in situations where stronger immune response is required to eradicate infection.

The development of miRNA-based therapies would represent novel approach to treating H. pylori infection, with potential for greater specificity and fewer side effects compared

to traditional therapies. However, translating possibilities into clinical practice will require extensive research and development of safe and effective delivery mechanisms for miRNA-based drugs.

❖ **Research Gaps and Future Studies**

While roles of miRNA-146a and miRNA-125b in H. pylori infection are becoming clearer, significant gaps remain in our understanding of how miRNAs interact with each other and with other components of immune system during course of infection, particularly in children.

One key area requires further investigation is precise mechanisms by which miRNA-146a and miRNA-125b regulate immune responses in pediatric H. pylori infection. Most studies to date have been conducted in adult populations or in vitro models, and there is need for more research focused specifically on children. Understanding how miRNAs function in developing immune system could provide critical insights into age-specific differences in pathogenesis of H. pylori infection and inform development of pediatric-specific diagnostic and therapeutic strategies.

Another important research gap is potential interaction between miRNA-146a, miRNA-125b, and other miRNAs or molecular pathways involved in H. pylori infection. immune response to H. pylori is highly complex, and it is likely miRNAs are part of larger network of regulatory molecules work together to control inflammation and immune responses. Mapping out network and identifying key interactions will be essential for understanding full scope of miRNA involvement in H. pylori infection.

Future studies should also explore feasibility of using miRNA-146a and miRNA-125b as therapeutic targets. will involve not only validating their roles in H. pylori infection but also developing effective delivery systems for miRNA-based therapies and conducting preclinical and clinical trials to assess their safety and efficacy in pediatric populations.

In conclusion, while there is considerable potential for miRNA-146a and miRNA-125b to be used as biomarkers and therapeutic targets in management of H. pylori infection, particularly in children, further research is needed to fully realize possibilities. Addressing current research gaps and conducting future studies focused on miRNAs will be crucial steps toward improving diagnosis, treatment, and prevention of H. pylori-related diseases in pediatric populations.

Conclusions

miRNA-146a and miRNA-125b play critical roles in modulating immune response to H. pylori infection in children, potentially influencing disease severity and outcomes. miRNAs show promise as biomarkers for diagnosing and predicting progression of H. pylori-associated diseases. Furthermore, miRNA-based therapies targeting miRNA-146a and miRNA-125b could represent innovative approaches to managing H. pylori infection, particularly in pediatric populations. However, further research is necessary to fully elucidate their roles and develop effective clinical applications.

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