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MINIREVIEWS

Role of nickel-regulated small RNA in modulation of *Helicobacter pylori* virulence factors

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Abstract

Helicobacter pylori (H. pylori) is a Gram-negative bacterium that infects about half of the world's population. *H. pylori* infection prevails by several mechanisms of adaptation of the bacteria and by its virulence factors including the cytotoxin associated antigen A (CagA). CagA is an oncoprotein that is the protagonist of gastric carcinogenesis associated with prolonged *H. pylori* infection. In this sense, small regulatory RNAs (sRNAs) are important macromolecules capable of inhibiting and activating gene expression. This function allows sRNAs to act in adjusting to unstable environmental conditions and in responding to cellular stresses in bacterial infections. Recent discoveries have shown that nickel-regulated small RNA (NikS) is a post-transcriptional regulator of virulence properties of *H. pylori*, including the oncoprotein CagA. Notably, high concentrations of nickel cause the reduction of NikS expression and consequently this increases the levels of CagA. In addition, NikS expression appears to be lower in clinical isolates from patients with gastric cancer when compared to patients without. With that in mind, this minireview approaches, in an accessible way, the most important and current aspects about the role of NikS in the control of virulence factors of *H. pylori* and the potential clinical repercussions of this modulation.

Key Words: *Helicobacter pylori*; Small regulatory RNAs; Nickel-regulated small RNA; Virulence factors; Cytotoxin associated antigen A; Gastric cancer

Core Tip: This paper aims to review current information about the role of nickel-regulated small RNA (NikS) in the modulation of main *Helicobacter pylori* virulence factors, specially cytotoxin associated antigen A (CagA), which is crucial to gastric cancer development. Here we explore what is the most important about the epigenetic processes involved in the interaction between nickel levels, NikS, and CagA and their potential clinical repercussions.

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INTRODUCTION

Helicobacter pylori (H. pylori) is a microaerophilic, Gram-negative, helical-shaped bacterium that inhabits the gastric environment of 60.3% of the world's population[1,2]. The infection is associated with the development of chronic gastritis, gastric and duodenal peptic ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[3]. In order to achieve a successful colonization, *H. pylori* must take advantage of some pathogenicity mechanisms, such as motility, adherence, manipulation of the gastric microenvironment, and virulence factors, of which we highlight cytotoxin associated antigen A (CagA), vacuolating cytotoxin A (VacA), and outer membrane proteins (OMPs). In this sense, the classification of this bacterium as a class I carcinogen is mostly due to the pro-oncogenic role of these virulence factors, especially CagA[4]. This oncoprotein is capable of inducing genetic, epigenetic, and morphological changes in gastric cells, including alterations of cell polarity and cytoskeleton, leading to "hummingbird" phenotype and promotion of genomic instability, which favor carcinogenesis[5-8]. In this regard, it has been recently discovered that nickel-regulated small RNA (NikS) plays a key role in gene expression during *H. pylori* infection, given that, through base pairing, it is able to repress CagA and VacA at the post-transcriptional level[9,10]. Notably, the expression of this sRNA is modulated by the nickel-responsive transcriptional regulator (NikR), consequently rendering *H. pylori* virulence factor expression dependent on nickel levels[10]. Therefore, considering that these virulence factors are associated with the onset of a carcinogenic process, the possible correlation between NikS expression and the development of gastric diseases secondary to *H. pylori* infection, including gastric carcinoma and MALT lymphoma, is indisputable. The present paper is a minireview that aims to gather, through an accessible perspective, important and current information regarding the role of a small regulatory RNA (sRNA), NikS, in the control of virulence factors of *H. pylori*, addressing the epigenetic processes involved and the potential clinical repercussions of this modulation.

SMALL REGULATORY RNAS

sRNAs are effective regulatory macromolecules that are able to modulate protein expression and function in response to environmental factors, such as pH, temperature, and metabolite concentration [11]. These post-transcriptional regulators of gene expression play a pivotal role in successful bacterial colonization and stress response, given that they enable metabolic adaptation to the host microenvironment and regulate the expression of virulence factors[12]. The three main classes of sRNAs comprise: (1) *Cis*-encoded antisense sRNAs; (2) *Trans*-encoded sRNAs; and (3) sRNAs that modify protein activity (Table 1)[13]. *Cis*-encoded antisense sRNAs are synthesized from the complementary strand of the mRNA that they modulate. Indeed, these regulators have been strongly associated with the repression of bacterial toxic proteins, through inhibition of primer maturation, transcriptional attenuation, and translational repression or promotion of RNA degradation[14,15]. In contrast, *trans*-encoded sRNAs are transcribed from a promoter somewhere else on the bacterial chromosome and are only partly complementary to their target mRNAs[16]. In general, this class of sRNAs mainly interfere with translational initiation and/or elongation, *e.g.*, by pairing to ribosome binding sites or translational enhancers. The translation impairment frequently leads to degradation of the mRNA, since it can be more easily targeted by ribonucleases (RNases)[17]. Lastly, sRNAs that modify protein activity are known to modulate protein activity by a mimicking mechanism and thus compete with RNA and DNA targets [13]. These mechanisms are described to utilize several auxiliary proteins, including RNases and ribosome-binding proteins. The Hfq RNA chaperon protein, for example, is strongly associated with the base-pairing between *trans*-encoded RNAs and their target mRNAs, hence acting in the regulation of virulence factors in Gram-negative bacteria[18].

Table 1 Regulatory bacterial sRNA groups and their characteristics

sRNA group	Characteristics	Ref.
Cis-encoded sRNAs	Repress genes encoding toxic proteins	Brantl[15]
Trans-encoded sRNAs	Modulate mRNA stability and translation	Brantl[15], Brantl and Müller[16]
sRNAs that modify protein activity	Mimic proteins and compete with RNA and DNA targets	Svensson and Sharma[17]

Thus, as mentioned above, post-transcriptional regulatory macromolecules known as sRNAs can stimulate or inhibit gene expression, playing a key role in bacterial infection through its three distinct groups, ranging from preventing ribosomal binding to modifying protein activities.

ROLE OF SRNAS IN BACTERIAL PATHOGENS

Hosts have evolved refined techniques to sense and react against pathogens, such as recognition of pathogen-associated molecular patterns that promotes activation of Toll-like receptors[19]. In this sense, the decisive pathogen's actions for the infection's success are a faster response and efficient adjustment to a continuously changing hostile environment. Those responses are regulated by sRNAs, due to their flexibility to target a plethora of genes or transcription factors, influencing many ambits of expression and responses to environmental stress[20]. Besides this, sRNAs do not require translation, which means a lower energy consumption for the pathogen[21].

As mentioned above, when entering the host, the bacterium faces diverse innate immunity barriers including: Temperature, pH, changes in nutrient availability, and physical barriers. It is during these circumstances when the varied toolkit of activities of sRNAs perform their roles for pathogen's survival [22]. These functions can be grouped in two main related fields: Management of biological processes, such as temperature response, biofilm formation, quorum sensing and virulence, and regulation of responses *vs* host barriers to infection, *e.g*., acidic pH, inflammation, and nutritional immunity[21].

Regarding the temperature response, it is known that pathogens have to evade the hyperthermia feedback during inflammation[23]. According to studies, an intense involvement of sRNAs in temperature adaptation has been noticed, helping the bacteria to regulate faster their physiology facing environmental thermal disorders[6]. For example, in analysis of *Borrelia burgdorferi*, responsible for Lyme disease, it was observed that a large set of sRNAs were entangled in regulation of genes involved in adaptation to pyrexia and identification of the molecular scheme to trigger according to environment [24].

Concerning biofilm formation, it is established that it requires coordination of quorum sensing mechanisms to succeed. In *P. aeruginosa*, researchers found a group of sRNAs, specially RhlS, that bind to the 5′ untranslated region (UTR) of *rhlI* mRNA and stabilizes it, which is Hfq dependent, resulting in the activation of biofilm genes according to the state of infection and offering additional protection against the host immune system[25].

The role of sRNAs in pathogen's virulence is also well-represented in *P. aeruginosa.* The gene *RpoS* commands a diverse number of virulence related genes, and its translation has been observed to be regulated by the sRNA ReaL, also a Hfq dependent base pairing apparatus, refining the bacterial virulence factors[26].

In the second category group, one of the first barriers to infection is the acidic pH. To overcome the acidic environment of the human stomach and to reach out host cells, for example, it involves several colonization factors like motility and chemotaxis[14]. In this context, *H. pylori* has sRNAs like RepG and 5′*ureB* that regulate expression of chemotaxis receptors contributing to stomach colonization[27,28] and linking urease production to surrounding pH[29].

A recent study reported that extreme conditions related to the stress caused by the host inflammatory response during oxidative burst, induces a heavy expression of RsaC, a sRNA of *Staphylococcus aureus,* avoiding the synthesis of an ineffective enzyme (sodA)[30]. The RsaC attaches to the start codon of the *sodA* mRNA, committed in protection against reactive oxygen species, leading to repression of this enzyme and allowing the transcription of a second enzyme, sodM, that uses iron as cofactor instead of manganese, recovering the oxidative protection[21]. Therefore, it is firmly established that sRNAs are key players in the adjustment to unstable environmental conditions and response to distinct cellular stresses.

POST-TRANSCRIPTIONAL REGULATION OF *H. PYLORI* VIRULENCE FACTORS BY NIKS

Recently, it was reported that the post-transcriptional regulation of *H. pylori* virulence factors depends on NikS. NikS has been described to act through base pairing in the 5′ UTR or coding sequence (CDS) of target mRNAs to repress gene expression, including the CagA oncoprotein[31]. In the past, NikS was believed to act as a *cis*-acting sRNA, however, Eisenbart *et al*[10] analyzed nucleotides upstream of transcriptional start sites of putative sRNAs and antisense RNAs and observed that NikS expression changed according to the length of a stretch of thymines (T) in the promoter region and these findings contrasted with the premise that NikS acted as a *cis*-acting sRNA[32]. Once it has been clarified that *H. pylori* also has *trans* sRNAs, it is important to highlight that they usually form a base pairing in the 5' UTR or RNA encoding target mRNAs modulating gene expression at the post-transcriptional level[18]. Eisenbart *et al*[10] also demonstrated in their NikS study that the thymine stretch of the *NikS*-10 box varies in different strains of *H. pylori* and this in turn has the potential to alter the spacing between box-10 and other promoter elements. Subsequently, the authors employed Northern blot analysis in the study which revealed differences in NikS expression from 16 to 7 Ts with the lowest expression at 12 Ts. This finding further corroborated the idea that NikS transcription suffers effects from the length variation of hypermutable single sequence repeats[10].

In this sense, Eisenbart *et al*[10] demonstrated that NikS represses the expression of the main virulence factors produced by *H. pylori* (CagA and VacA) and three additional factors (HofC, HorF, and HPG27_1238) related to the pathogenicity of the G27 strain, through interactions of base pairing[6]. Completely, Kinoshita-Daitoku *et al*[32] were responsible for one of the main current studies on NikS. They identified eight factors downregulated by NikS including CagA, HofC, HELPY_1262, HP0410, HorB, OMP14, HopE, and HP1227 and noted that the impact on the regulation of CagA expression stood out among the other factors[32]. Since the regulatory process performed by NikS acts on target mRNAs repressing or activating post-transcriptional gene expression, it is important to say that *H. pylori* resorts to endoribonucleases such as RNase III so that the sRNAs degrade the target mRNA leading to translation inhibition[18]. In this aspect, Kinoshita-Daitoku *et al*[32] also reported that NikS regulates the oncoprotein CagA by binding to multiple binding sequences present in its CDS region causing mRNA degradation by RNase III. Furthermore, the authors observed that NikS binding to CagA mRNA regulated the amount of interleukin-8 (IL-8) secreted in *H. pylori* infection, indicating that NikS acts in the functional control of CagA[32].

Moreover, it is known that VacA is a multifunctional toxin, which stands out mainly for cell vacuolation. In this sense, the repression of this virulence factor can impact the persistence of *H. pylori* infection[33]. The expression of OMPs in *H. pylori* strains, in turn, also contributes to bacterial pathogenicity through different mechanisms, such as adhesion, penetration of the defense barrier, and evasion of the immune system. In this sense, by repressing the biosynthesis of OMPs, such as HofC and HorF, the adhesion and colonization processes can be compromised[34].

Finally, it is important to mention that the integration between nickel availability and NikS expression is performed through the NikR[35]. When cytoplasmic nickel concentrations reach a certain threshold, the NikR protein represses nickel import mechanisms in order to control the availability of the metal and achieve the necessary homeostasis[36]. However, NikR also regulates the expression of other genes associated with nickel homeostasis by binding to NikR operators in the promoter or upstream regions[37]. For example, NikR has been shown to bind directly to the NikS promoter, being a key player in controlling NikS expression. In addition, researchers analyzed how strains with varying sizes of T stretch in the promoter region responded to changes in nickel concentration or NikR deletion. Their results showed that the addition of nickel caused a 2- to 10-fold decrease in NikS expression while the deletion of NikR led to a 2-fold increase in NikS levels[6]. In this way, NikS is transcriptionally repressed by nickel *via* NikR since NikR is able to ration nickel availability and reduced concentrations of this metal imply higher levels of NikS, thereby inhibiting the expression of *H. pylori* virulence factors (*e.g.* CagA) (Figure 1). Furthermore, NikS expression changed in nickel-added strains according to different T stretch lengths, but there was no direct correlation between these two factors[6].

POTENTIAL CLINICAL REPERCUSSION OF MODULATION OF CAGA EXPRESSION VIA POST-TRANSCRIPTIONAL CONTROL BY NIKS

CagA is a translocated effector protein that induces morphofunctional modifications in gastric epithelial cells and an inflammatory response, which lead, respectively, to increased bacterial adhesion and nutrient uptake[38,39] (Figure 2). This oncoprotein is encoded by the *Cag*A gene, which is a marker of the *cag* PAI, a 40 kb DNA fragment that contains about 31 genes and is present in more virulent strains of *H. pylori*. Some genes on this mobile region of the chromosome encode proteins that form a type IV secretion system, which is responsible for translocating the CagA protein into the cytoplasm of host cells [40-44]. The C-terminal region of CagA has a variable number of Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs, which serve as tyrosine phosphorylation sites. Once it reaches the host cell cytosol, the EPIYA sites of the effector protein are phosphorylated by Src family kinases such as s-Src, Fyn, Lyn, and Yes or by Abl

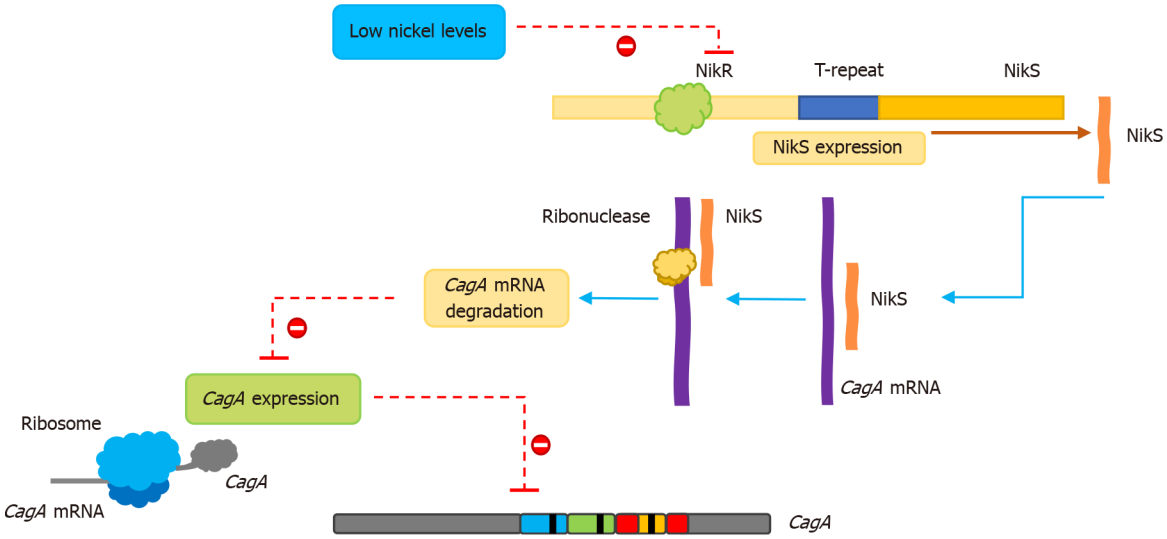

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Figure 1 Nickel-regulated small RNA regulates the expression of cytotoxin associated antigen A depending on nickel availability. NikR: Nickel-responsive transcription factor; NikS: Nickel-regulated sRNA; *CagA*: Cytotoxin-associated gene A.

kinases[45,46]. Afterward, CagA acts as a promiscuous scaffold protein that simultaneously disturbs multiple intracellular signaling cascades, involved in regulation of a large range of cellular processes, including proliferation, differentiation, and apoptosis[47].

Phosphorylated CagA is able to stimulate cell proliferation through the activation of promitogenic signaling pathways. Among these, we highlight the activation of the ERK-MAPK pathway through binding to the Src-homology domain 2 and consequent activation of SHP-2[48]. This process also leads to alterations in the cytoskeleton, which induces host cell elongation and change to the recognized "hummingbird" phenotype[7,8,49]. In addition, CagA causes disruption of cell polarity by interaction with the serine-threonine kinase Par-1b and disturbs cell junction-mediated functions[8,47]. This virulence factor is also able to reduce apoptosis in gastric epithelial cells, through the inhibition of tumor suppressor factors such as p53 and RUNX3[50-53]. These direct effects of CagA on epithelial cells could be related to the development of precancerous lesions, since carcinoma development has been observed in animal models even in the absence of inflammation[54-56]. Nevertheless, this effector protein was reported to be able to induce the transcription factor NF-κB and IL-8, which are crucial determinants of chronic inflammation and thus of the pathogenesis of peptic ulcer and gastric cancer[43,57]. At last, CagA also induces genetic and epigenetic alterations in the host cells that lead to a pro-carcinogenic environment[7].

In this regard, some authors suggest that the modulation of CagA expression *via* post-transcriptional control by NikS favors a more delicate equilibrium between induction of morphofunctional changes and inflammatory response with its regulation, so as to establish a balance between eradication and nutrient uptake[54]. Using *in vitro* infection studies, Eisenbart *et al*[10] demonstrated that possibly due to increased CagA expression, G27 strains deficient in NikS show higher numbers of intracellular bacteria, greater "hummingbird" phenotype induction in host cells, as well as increased epithelial barrier disruption. From these findings, it is possible to infer that higher expression of NikS and, consequently, lower synthesis and translocation of the oncoprotein, would reduce the CagA-induced morphofunctional alterations in the host cell, such as apoptosis of epithelial cells, loss of cell polarity, and chronic NF-κB-dependent inflammatory response, along with carcinogenesis. Interestingly, it was further reported by Kinoshita-Daitoku *et al*[32] that NikS expression is lower in clinical isolates from gastric cancer patients than in isolates derived from non-cancer patients, while the expression of NikS-targeted virulence factors, including CagA, is higher in isolates from gastric cancer patients. Therefore, it is possible to suggest a possible correlation between NikS expression and the onset of peptic ulcer and gastric malignancies, such as gastric carcinoma and MALT lymphoma secondary to *H. pylori* infection.

FUTURE PERSPECTIVES ON REGULATION OF NIKS OVER *H. PYLORI* VIRULENCE

Considering that the regulatory role of NikS on *H. pylori* virulence factors is a recent discovery, there are still few studies on the subject. However, the broad action of NikS on these virulence factors may be strongly related to the risk of diseases derived from *H. pylori* infection. In this sense, one of the aims of our group is to evaluate whether the variation of the number of Ts in the promoter region of the *NikS* gene is associated with the risk of duodenal ulcer or gastric carcinoma in adults. However, further

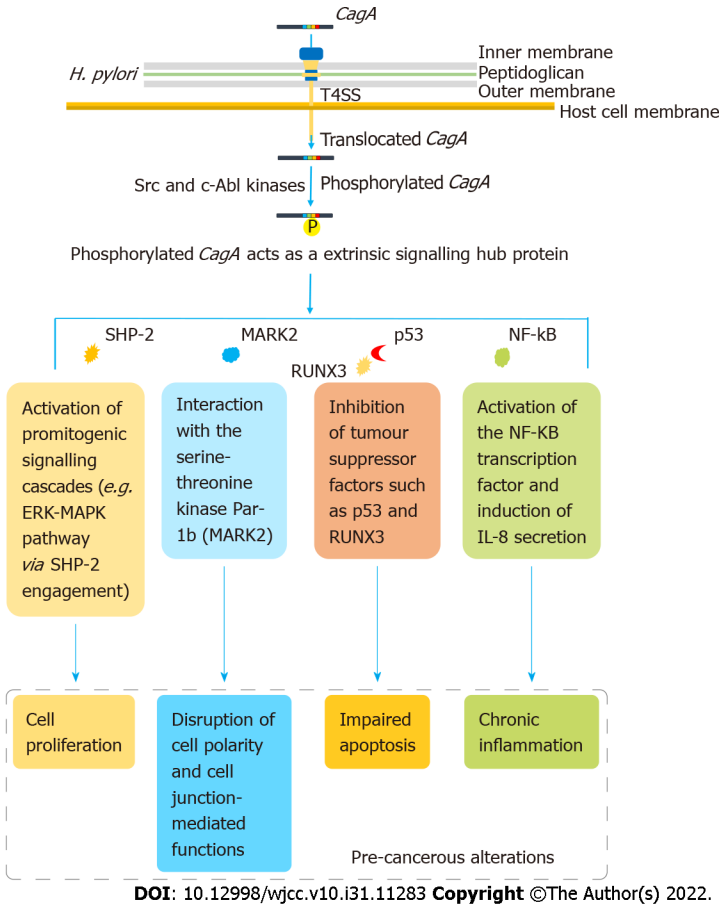

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Figure 2 Simplified molecular mechanisms of cytotoxin associated antigen A mediated carcinogenesis. After the phosphorylation process, cytotoxin associated antigen A acts as a promiscuous scaffold or hub protein that simultaneously disturbs multiple host signaling pathways, involved in regulation of a large range of cellular processes, including proliferation, differentiation, and apoptosis. Moreover, cytotoxin associated antigen A is also able to induce NF-kB-mediated chronic inflammation. Ultimately, the disharmonic interaction between cytotoxin associated antigen A and host proteins leads to pre-cancerous cellular alterations. *CagA*: Cytotoxin-associated gene A; *H. pylori*: *Helicobacter pylori*; IL-8: Interleukin-8.

studies are still required for better understanding the role of NikS in the pathogenesis of *H. pylori*, as well as its possible relationship with other genes.

CONCLUSION

In summary, recent findings on sRNA-mediated regulation of *H. pylori* infection revealed that increased nickel concentrations lead to reduced NikS expression and this in turn up-regulates CagA levels. There is still much to be clarified about the regulatory properties involved in *H. pylori* infection. However, it is notable that CagA is the protagonist of gastric carcinogenesis and a deeper understanding of the interaction between this virulence factor and sRNAs such as the nickel-dependent NikS is of utmost importance for a broader understanding of the mechanisms involved in the control mediated by RNAs in *H. pylori* and their association with gastric malignancies and other clinical conditions. Finally, given the potential for heterogeneity of the bacterium, evolution of its strains, its pathogenicity, and the emergence of therapeutic resistance of this pathogen, it is essential to periodically reassess the molecular issues of the infection to achieve advances in the diagnosis and treatment of the disease.

FOOTNOTES

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